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(19)(CA) **CANADIAN PATENT** (12)

(54) Benzazepine and Benzazepinone Derivatives

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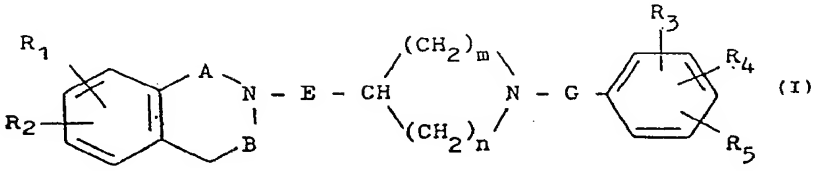
ABSTRACT 1321194

This invention relates to a novel compound of formula I



(I)

(wherein
A represents a $-CH_2-CH_2-$, $-CH=CH-$, $-\overset{*}{C}H_2-CO-$ or $-NH-\overset{*}{C}O-$ group, and

B represents a methylene, carbonyl or thiocarbonyl group, or

A represents a $-CO-CO-$ or $-\overset{OH}{\overset{|}{\overset{*}{C}}}H-CO-$ group and B represents a methylene group, the mark * signifying that the carbon or nitrogen atom so marked is bonded to the phenyl ring;

E represents a straight-chained alkylene group with 1 to 3 carbon atoms optionally substituted by an alkyl group with 1 to 3 carbon atoms;

G represents a group G_1G_2 optionally substituted by an alkyl group with 1 to 3 carbon atoms and wherein G_1 represents a straight-chained alkylene group with 1 to 5 carbon atoms and G_2, which is adjacent to the phenyl ring, represents a bond linking G_1 to the phenyl ring or, where G_1 represents a straight-claimed alkylene group with 2 to 4 carbon atoms, an oxygen or sulphur atom or an imino, methylimino, sulphinyl or sulphonyl group;

R_1 represents a hydrogen or halogen atom or, a trifluoromethyl, nitro, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy or phenylalkoxy group, wherein any alkyl moiety in R_1 contains from 1 to 3 carbon atoms, and

R_2 represents a hydrogen or halogen atom, or a hydroxy, alkoxy, phenylalkoxy or alkyl group, wherein any alkyl moiety in R_2 contains from 1 to 3 carbon atoms, or

R_1 and R_2 together represent an alkylenedioxy group with 1 or 2 carbon atoms;

R_3 represents a hydrogen or halogen atom, or an alkyl group with 1 to 3 carbon atoms, or an alkoxy group with 1 to 3 carbon atoms, or a hydroxy, nitro, cyano or trifluoromethyl group, and

R_4 represents a hydrogen atom, or an amino group, or an alkoxy, alkanesulphonyloxy, alkylamino or dialkylamino group with 1 to 3 carbon atoms in the or each alkyl moiety or an alkanoylamino group with 2 or 3 carbon atoms in the alkanoyl moiety; or

R_3 and R_4 together represent an alkylenedioxy group with 1 or 2 carbon atoms;

R_5 represents a hydrogen or halogen atom, or a hydroxy group, or an alkyl or alkoxy group with 1 to 3 carbon atoms in the alkyl moiety;

m represents the number 1, 2, 3, 4 or 5, and

n represents the number 0, 1 or 2, with the proviso that the sum of n and m is 3, 4 or 5);

the enantiomers, diastereomers and acid addition salts thereof.

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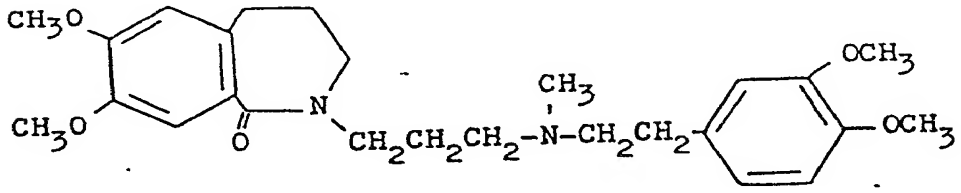
The present invention relates to novel cyclic amine derivatives and their enantiomers, diastereomers and physiologically acceptable acid addition salts which produce valuable pharmacological effects such as lowering the heart rate.

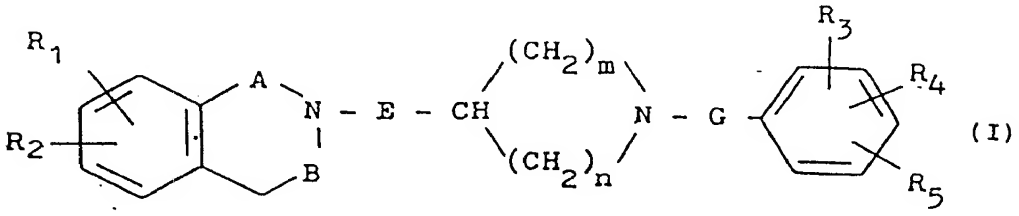
British Patent No. 1 548 844 describes, inter alia, the compound of formula



and the physiologically acceptable acid addition salts thereof. These compounds are said to have valuable pharmacological properties, namely a mild hypotensive activity and, more particularly, a selective heart rate-reducing activity.

We have now found that certain novel cyclic amine derivatives, and salts thereof surprisingly have even more valuable pharmacological properties, namely a long-lasting heart rate reducing activity and the effect of reducing the oxygen requirements of the heart.

According to one aspect of the present invention we thus provide compounds of formula I



(I)

(wherein

A represents a $-CH_2-CH_2-$, $-CH=CH-$, $-\overset{*}{C}H_2-CO-$ or $-\overset{*}{N}H-CO-$ group and

B represents a methylene, carbonyl or thiocarbonyl group, or

A represents a $-CO-CO-$ or $-\overset{OH}{\underset{|}{\overset{*}{C}}}H-CO-$ group and B represents a methylene group, the mark * signifying that the carbon or nitrogen atom so marked is bonded to the phenyl ring;

E represents a straight-chained alkylene group with 1 to 3 carbon atoms optionally substituted by an alkyl group with 1 to 3 carbon atoms;

G represents group G_1G_2 optionally substituted by an alkyl group with 1 to 3 carbon atoms and wherein G_1 represents a straight-chained alkylene group with 1 to 5 carbon atoms and G_2, which is adjacent to the phenyl ring, represents a bond linking G_1 to the phenyl ring or, where G_1 represents a straight chained alkylene group with 2 to 4 carbon atoms, an oxygen or sulphur atom or an imino, methylimino, sulphinyl or sulphonyl group;

R_1 represents a hydrogen or halogen atom, or a trifluoromethyl, nitro, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy or phenylalkoxy group, wherein any alkyl moiety is R_1 contains from 1 to 3 carbon atoms, and

R_2 represents a hydrogen or halogen atom, or a hydroxy, alkoxy, phenylalkoxy or alkyl group, wherein any alkyl moiety in R_2 contains from 1 to 3 carbon atoms, or

R_1 and R_2 together represent an alkylenedioxy group with 1 or 2 carbon atoms;

R_3 represents a hydrogen or halogen atom, or an alkyl group with 1 to 3 carbon atoms, or an alkoxy group with 1 to 3 carbon atoms, or a hydroxy, nitro, cyano or trifluoromethyl group, and

R_4 represents a hydrogen atom, or an amino group, or an alkoxy, alkanesulphonyloxy, alkylamino or dialkylamino group with 1 to 3 carbon atoms in the or each alkyl moiety or an alkanoylamino group with 2 or 3 carbon atoms in the alkanoyl moiety, or

R_3 and R_4 together represent an alkylenedioxy group with 1 or 2 carbon atoms;

R_5 represents a hydrogen or halogen atom, or a hydroxy group, or an alkyl or alkoxy group with 1 to 3 carbon atoms in the alkyl moiety;

m represents the number 1, 2, 3, 4 or 5, and

n represents the number 0, 1 or 2, with the proviso that the sum of n and m is 3, 4 or 5),

the enantiomers, diastereomers and acid addition salts thereof, preferably the physiologically acceptable acid addition salt thereof.
Thus in formula I G may represent a straight-chained alkylene group with 1 to 5 carbon atoms optionally substituted by an alkyl group with 1 to 3 carbon atoms, or a straight-chained alkylene group with 3 to 5 carbon atoms optionally substituted by an

alkyl group wherein a methylene group, adjacent to the phenyl nucleus, is replaced by an oxygen or sulphur atom or by an imino, methylimino, sulphinyl or sulphonyl group.

Examples of the definitions given for the groups hereinbefore include:

for R_1- a hydrogen, fluorine, chlorine or bromine atom or a methyl, ethyl, n-propyl, isopropyl, trifluoromethyl, hydroxy, methoxy, ethoxy, n-propoxy, isopropoxy, nitro, amino, methylamino, ethylamino, n-propylamino, isopropylamino, dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, methyl-ethylamino, methyl-n-propylamino, methyl-isopropylamino, ethyl-n-propylamino, benzyloxy, 1-phenylethoxy, 1-phenylpropoxy, 2-phenylethoxy or 3-phenylpropoxy group;

for R_2- a hydrogen, chlorine or bromine atom or a methyl, ethyl, n-propyl, isopropyl, hydroxy, methoxy, ethoxy, n-propoxy, isopropoxy, benzyloxy, 1-phenylethoxy, 2-phenylethoxy, 2-phenylpropoxy or 3-phenylpropoxy group or together with R_1 a methylenedioxy or ethylenedioxy group;

for R_3- a hydrogen, fluorine, chlorine or bromine atom or a methyl, ethyl, n-propyl, isopropyl, hydroxy, methoxy, ethoxy, n-propoxy, isopropoxy, nitro, cyano or trifluoromethyl group:

for R_4- a hydrogen atom or a methoxy, ethoxy, n-propoxy, isopropoxy, methanesulphonyloxy, ethanesulphonyloxy, n-propanesulphonyloxy, amino, methylamino, ethylamino, n-propylamino, isopropylamino, dimethylamino, diethylamino, di-n-propylamino, diisopropylamino, methylethylamino, methyl-n-propylamino, methyl-isopropylamino, ethyl-n-propylamino, acetylamino

or propionylamino group or together with R_3 a methylenedioxy or ethylenedioxy group;

for R_5- a hydrogen, chlorine or bromine atom or a methyl, ethyl, n-propyl, isopropyl, hydroxy, methoxy, ethoxy, n-propoxy or isopropoxy group;

for E- a methylene, ethylene, n-propylene, ethylidene, n-propylidene, n-butylidene, 2-methyl-n-propylidene, 1-methyl-ethylene, 1-ethyl-ethylene, 2-methyl-ethylene, 2-ethyl-ethylene, 1-n-propyl-ethylene, 1-methyl-n-propylene, 2-methyl-n-propylene, 3-methyl-n-propylene, 1-ethyl-n-propylene, 2-n-propyl-n-propylene or 3-ethyl-n-propylene group; and

for G- a methylene, ethylidene, n-propylidene, n-butylidene, 2-methyl-propylidene, ethylene, 1-methyl-ethylene, 1-ethyl-ethylene, 1-propyl-ethylene, 2-methyl-ethylene, 2-ethyl-ethylene, n-propylene, n-butylene, n-pentylene, 1-methyl-n-propylene, 1-methyl-n-butylene, 1-methyl-n-pentylene, 1-ethyl-n-propylene, 2-ethyl-n-propylene, 1-ethyl-n-butylene, ethyleneoxy, n-propyleneoxy, n-butyleneoxy, ethylenethio, n-propylenethio, n-butylenethio, ethylenesulphinyl, ethylenesulphonyl, n-propylenesulphinyl, n-propylenesulphonyl, n-butylenesulphinyl, ethyleneamino, n-propyleneamino, n-butyleneamino, N-methyl-ethyleneamino, N-methyl-n-propyleneamino or N-methyl-n-butyleneamino group.

By way of example, the following are compounds which fall within the scope of the present invention:

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-thione;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-1,2-dione;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1-hydroxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-amino-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-acetamino-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-amino-3,5-dibromo-phenoxy)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3,4-dimethoxy-benzyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3-nitro-4-acetamino-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4,5-trimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-methoxy-phenyl)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(n-(2-(4-nitro-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3-methyl-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3-methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-methyl-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-bromo-phenyl)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-hexahydro-azepin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-amino-3,5-dibromo-phenoxy)-propyl)-hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-hexahydro-azepin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-methylenedioxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3,4-dichloro-benzyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(3-methoxy-phenoxy)-propyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(3-methyl-phenoxy)-propyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-amino-3,5-dichloro-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3,4-methylenedioxy-phenoxy)-propyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(4-(4-methoxy-phenyl)-butyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(phenoxy)-ethyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-methoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(4-methoxy-phenyl)-methyl)-piperidin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3,4-dimethoxy-phenyl)-methyl)-piperidin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-nitro-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3-trifluoromethylphenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(3,5-dimethoxy-phenoxy)-propyl)-piperidin-2-yl)-ethyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3-methoxy-4-methanesulphonyloxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-benzyloxy-3-methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[N-(2-(2-fluorophenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[N-(2-(4-fluorophenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-hexahydro-azepin-2-yl)-ethyl-2]-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-amino-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-amino-3,5-dibromo-phenoxy)-propyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3,4-dimethoxy-benzyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4,5-trimethoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-methoxy-phenyl)-propyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-methoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-nitro-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[N-(2-(3-methyl-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3-methoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-methyl-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-bromo-phenyl)-propyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7-methoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7-trifluoromethyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7-methylamino-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7-dimethylamino-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dichloro-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7-methylamino-8-methoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7-bromo-8-methoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7-chloro-8-methoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7-hydroxy-8-methoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-piperidin-3-yl)-methyl]-7-methoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-piperidin-3-yl)-methyl]-7-trifluoromethyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-piperidin-3-yl)-methyl]-7-methylamino-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-piperidin-3-yl)-methyl]-7-dimethylamino-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-piperidin-3-yl)-methyl]-7,8-dichloro-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-piperidin-3-yl)-methyl]-7-methylamino-8-methoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-piperidin-3-yl)-methyl]-7-bromo-8-methoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-piperidin-3-yl)-methyl]-7-chloro-8-methoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-piperidin-3-yl)-methyl]-7-hydroxy-8-methoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(3,4-dimethoxy-phenyl)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one;

3-[(N-(2-(3,4-methylenedioxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one;

3-[(N-(2-(3-methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one;

3-[(N-(2-(4-methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one;

3-[(N-(2-(2-methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one;

3-[(N-(2-(N-(3,4-dimethoxy-phenyl)-methylamino)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-1,3-benzodiazepin-2-one;

3-[(N-(3-(3,4-dimethoxy-phenylthio)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylthioethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylaminoethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenoxyethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,5-dichloro-4-methoxy-phenoxy)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenylamino)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(3,4-dimethoxy-phenylsulphinyl)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(3,4-dimethoxy-phenylsulphonyl)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-dimethylamino-phenoxy)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-amino-3,5-dibromo-phenylsulphonyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-amino-3,5-dibromo-phenylsulphinyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-amino-3,5-dibromo-phenylthio)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dichloro-phenoxy)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenoxy)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(N-phenyl-N-methyl-amino)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-methoxy-phenoxy)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-methylenedioxy-phenoxy)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-amino-3,5-dichloro-phenylamino)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-hydroxy-3-methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-pyrrolidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-amino-3,5-dibromo-phenoxy)-propyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-methoxy-phenyl)-propyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-methoxy-phenyl)-ethyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3-methyl-phenyl)-ethyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3-methoxy-phenyl)-ethyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-nitro-phenyl)-ethyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-bromo-phenyl)-propyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(3-(4-bromo-phenyl)-propyl)-hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-nitro-phenyl)-ethyl)-hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-methoxy-phenyl)-ethyl)-hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-methyl-phenyl)-ethyl)-hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-phenylethyl)-hexahydro-azepin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(3-methyl-phenyl)-ethyl)-hexahydro-azepin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one;

3-[(N-(2-(4-fluoro-phenyl)-ethyl)-hexahydro-azepin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one; and

the enantiomers, diastereomers and acid addition salts thereof.

Preferred compounds of formula I above are those wherein

A, B, m and n are as hereinbefore defined;
E represents a methylene or ethylene group;

G represents a group G_1G_2 wherein G_1 represents a bond and G_2 represents an n-alkylene group with 1 to 4 carbon atoms, or wherein G_1 represents an ethylene or n-propylene group and G_2 represents an oxygen or sulphur atom or an imino, methylimino, sulphinyl or sulphonyl group;

R_1 represents a hydrogen, fluorine, chlorine or bromine atom, or a hydroxy, methoxy, trifluoromethyl, methylamino or dimethylamino group, and

R_2 represents a hydrogen, chlorine or bromine atom or a methoxy group, or

R_1 and R_2 together represent a methylenedioxy group;

R_3 represents a hydrogen, fluorine, chlorine or bromine atom or a methyl, hydroxy, methoxy or nitro group, and

R_4 represents a hydrogen atom or a methoxy, methanesulphonyloxy, amino or acetylamino group, or

R_3 and R_4 together represent a methylenedioxy group; and

R_5 represents a hydrogen, chlorine or bromine atom or a methoxy group;

and the enantiomers, diastereomers and acid addition salts thereof.

Particularly preferred compounds of formula I are those wherein

m and n are as hereinbefore defined;

A represents a $-CH_2CH_2-$ or $-CH=CH-$ group and B represents a methylene or carbonyl group, or

A represents a -CO-CO- group and B represents a methylene group;

E represents a methylene or ethylene group;

G represents an n-alkylene group with 2 to 4 carbon atoms, or an ethyleneoxy or n-propyleneoxy group;

R_1 represents a hydrogen atom or a methoxy group, and

R_2 represents a hydrogen atom or a methoxy group, or

R_1 and R_2 together represent a methylenedioxy group;

R_3 represents a hydrogen atom or a methyl, hydroxy or methoxy group, and

R_4 represents a hydrogen atom or a methoxy group, or

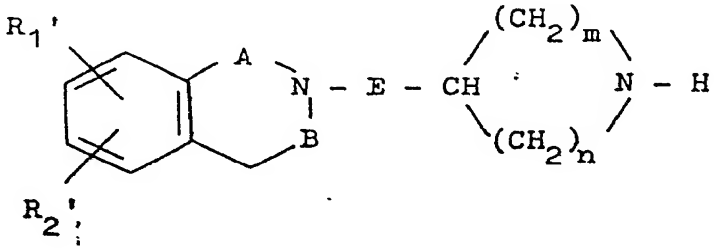
R_3 and R_4 together represent a methylenedioxy group; and

R_5 represents a hydrogen atom;

and the enantiomers, diastereomers and acid addition salts thereof.

According to a further aspect of the invention, we provide a process for the preparation of a compound of formula I as hereinbefore defined, which comprises at least one of the following steps:

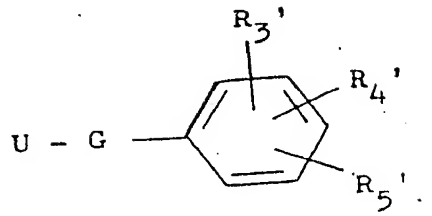
a) reacting a compound of formula II



(II)

(wherein
A, B, E, m and n are as hereinbefore defined,
R_1' represents a hydroxy, amino or C_{1-3} alkylamino group protected by a protecting group or has the meanings given for R_1 hereinbefore, and

R_2' represents a hydroxy group protected by a protecting group or has the meanings given hereinbefore) with a compound of formula III



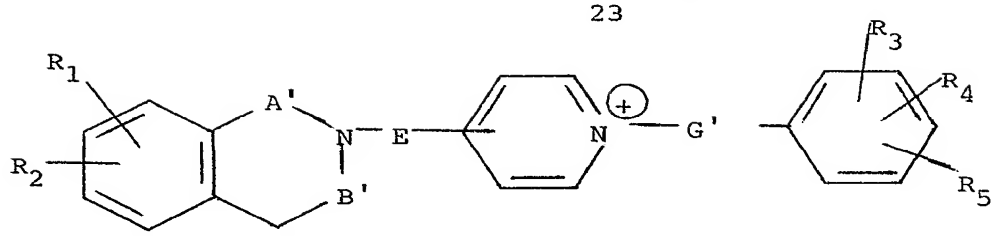
(III)

(wherein
R_3' represents a hydroxy group protected by a protecting group or has the meanings given for R_3 hereinbefore, R_4' represents an amino or C_{1-3} alkylamino group protected by a protecting group or has the meanings given for R_4 hereinbefore, R_5' represents a hydoxy group protected by a protecting group or has the meanings given for R_5 hereinbefore, and

U represents a nucleophilic leaving group such as a halogen atom or a sulphonyloxy group e.g. a chlorine, bromine or iodine atom, a methanesulphonyloxy, p-toluenesulphonyloxy or ethylsulphonyloxy group, and subsequently, if required, splitting off any protecting group used;

b) (to prepare a compound of formula I wherein G has the meanings given for G hereinbefore (with the exception of the groups containing a sulphenyl, sulphinyl or sulphonyl group), A represents a $-CH_2-CH_2$ group, B represents a methylene or carbonyl group and the sum of m and n is 4)

hydrogenating a compound of formula IV



(IV)

(wherein

R_1 to R_5 and E are as hereinbefore defined;

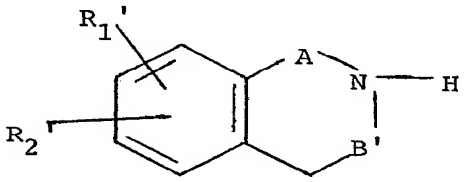
G' has the meanings given for G hereinbefore, with the exception of the groups containing a sulphur atom or a sulphinyl or sulphonyl group,

A' represents a -CH=CH- or $-CH_2CH_2$ group and

B' represents a methylene or carbonyl group;

c) (to prepare a compound of formula I wherein B represents a carbonyl or methylene group)

reacting a compound of formula V



(V)

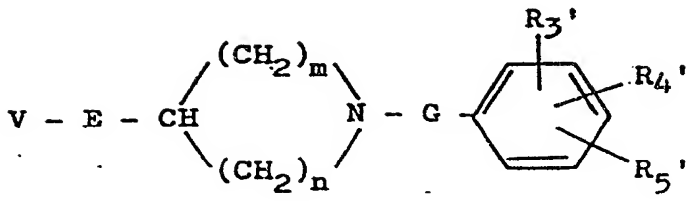
(wherein

A is as hereinbefore defined;

R_1' represents a hydroxy, amino or C_{1-3} alkylamino group protected by a protecting group or has the meanings given for R_1 hereinbefore;

R_2' represents a hydroxy group protected by a protecting group or has the meanings given for R_2 hereinbefore, and

B' represents a carbonyl or methylene group) with a compound of formula VI



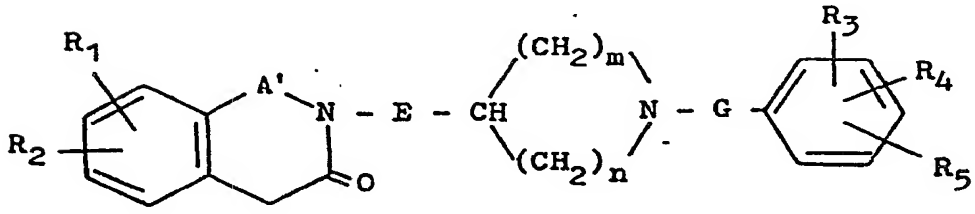
(VI)

(wherein
E, G, m and n are as hereinbefore defined;
R_3' represents a hydroxy group protected by a protecting group or has the meanings given for R_3 hereinbefore;
R_4' represents an amino or C_{1-3} alkylamino group protected by a protecting group or has the meaning given for R_4 hereinbefore, R_5' represents a hydroxy group protected by a protecting group or has the meanings given for R_5 hereinbefore, and

V represents a nucleophilically exchangeable group such as a halogen atom or a sulphonyloxy group, e.g. a chlorine, bromine or iodine atom, a methanesulphonyloxy, p-toluenesulphonyloxy or ethoxysulphonyloxy group) and subsequently, if required, splitting off any protecting group used;

d) (to prepare a compound of formula I wherein A represents a $-CH_2-CH_2$ or -CH=CH- group and B represents a thiocarbonyl group)

reacting a compound of formula VII

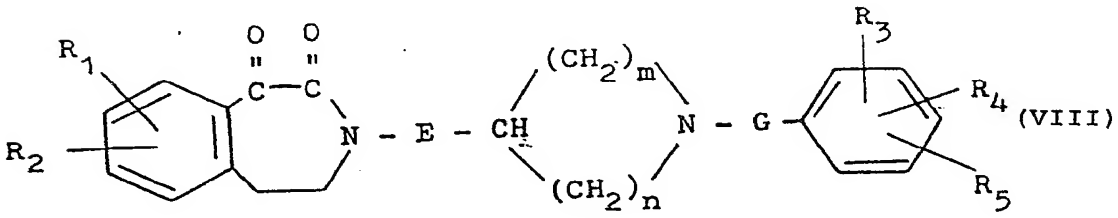


(VII)

(wherein
R_1 to R_5, E, G, m and n are as hereinbefore defined and A' represents a $-CH_2-CH_2$ or $-CH=CH-$ group) with a sulphurising agent;

e) (to prepare a compound of formula I wherein A represents a $-\overset{OH}{\overset{|}{C}}H-CO-$ group and B represents a methylene group)

reducing a compound of formula VIII

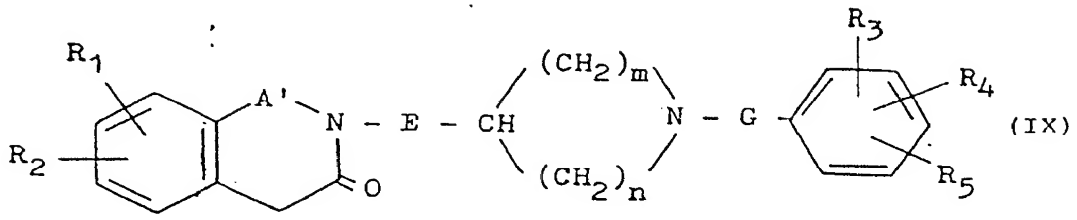


(VIII)

(wherein
R_1 to R_5, E, G, m and n are as hereinbefore defined);

f) (to prepare a compound of formula I wherein A represents a $-CH_2-CH_2-$ or $-CH=CH-$ group and B represents a methylene group)

reducing a compound of formula XI

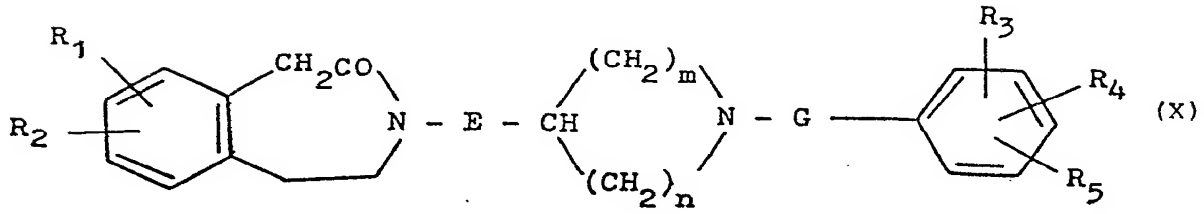


(IX)

(wherein
R_1 to R_5, E, G, m and n are as hereinbefore defined and A' represents a $-CH_2-CH_2-$ or $-CH=CH-$ group);

g) (to prepare a compound of formula I wherein A represents a $-COCO-$ group)

oxidizing a compound of formula X

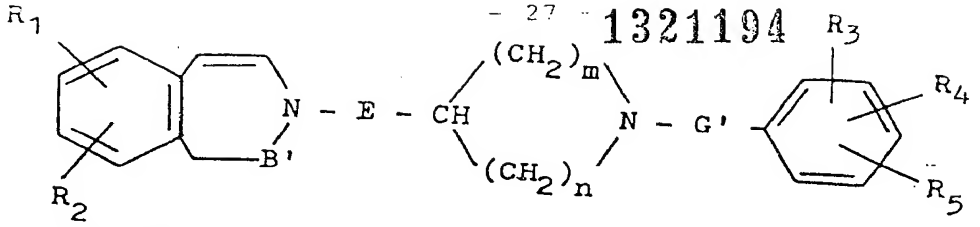


(X)

(wherein
R_1 to R_5, E, G, m and n are as hereinbefore defined);

h) (to prepare a compound of formula I wherein G has the meanings given for G hereinbefore (with the exception of the groups containing a sulphur atom or a sulphinyl or sulphonyl group), A represents a $-CH_2-CH_2-$ group and B represents a methylene or carbonyl group)

hydrogenating a compound of formula XI



(XI)

(wherein

R_1 to R_5, E, G, m and n are as hereinbefore defined;

G_1 has the meanings given for G hereinbefore, with the exception of the groups containing a sulphur atom or a sulphinyl or sulphenyl group, and

B' represents a methylene or carboxyl group);

i) reducing a compound of formula I (wherein R_1 and/or R_3 represents a nitro group) to a corresponding amino compound of formula I;

j) acylating a compound of formula I wherein R_4 represents a hydroxy or amino group to a corresponding alkanesulphonyloxy or alkanoylamino compound of formula I;

k) resolving a compound of formula I which contains at least one chiral centre into its diastereomers or into its enantiomers; and

l) converting a compound of formula I into an acid addition salt thereof, particularly a physiologically acceptable acid addition salt with inorganic or organic acids.

In the reaction of step (a) the protecting group used for a hydroxy group may be, for example, a trimethylsilyl, acetyl, benzoyl, benzyl or tetrahydropyranyl group and the protecting group used for an amino or alkylamino group may be an acetyl, benzoyl, ethoxycarbonyl or benzyl group.

The reaction of step (a) is conveniently carried out in a solvent or mixture of solvents such as acetone, diethylether, methylformamide, dimethylformamide, dimethylsulfoxide, benzene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran, dioxan or in an excess of the compounds of formulae II and/or III used. The reaction optionally is carried out in the presence of an acid binding agent, e.g. an alkoxide such as potassium tert.butoxide, an alkali metal hydroxide such as sodium or potassium hydroxide, an alkali metal carbonate such as potassium carbonate, an alkali metal amide such as sodium amide, an alkali metal hydride such as sodium hydride, a tertiary organic base such as triethylamine or pyridine, the latter of which may simultaneously also serve as a solvent. The reaction may optionally be carried out in the presence of a reaction accelerator such as potassium iodide depending on the reactivity of the nucleophilically exchangeable group, and conveniently is carried out at temperatures of between 0 and 150°C, preferably at temperatures of between 50 and 120°C, e.g. at the boiling temperature of the solvent used. However the reaction may also be carried out without a solvent. It is, however, particularly advantageous to perform the reaction in the presence of a tertiary organic base or an excess of the amine of formula III used.

The optional subsequent splitting off of a protecting group used is preferably carried out by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxan/water, in the presence of an acid such as hydrochloric or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide at temperatures of between 0 and 100°C, preferably at the boiling temperature of the reaction mixture. However,

a benzyl group is preferably split off by hydrogenolysis, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid, at temperatures of between 0 and 50°C, but preferably at ambient temperature, and under a hydrogen pressure of from 1 to 7 bar, preferably from 3 to 5 bar.

The hydrogenation of step (b) may conveniently be carried out in a solvent or mixture of solvents such as methanol, ethanol, ethyl acetate or glacial acetic acid with catalytically activated hydrogen, e.g. with hydrogen in the presence of platinum or palladium/charcoal, optionally in the presence of a base such as an alkoxide, e.g. sodium methoxide, under a hydrogen pressure of from 1 to 7 bar, preferably from 3 to 5 bar, and at temperatures of between 0 and 75°C, preferably at temperatures of between 20 and 50°C.

In the reaction of step (b) any benzyloxy group present may be converted into the corresponding hydroxy group.

In the reaction of step (c) suitable protecting groups for a hydroxy group include, for example, trimethylsilyl, acetyl, benzoyl, benzyl or tetrahydropyranyl groups and suitable protecting groups for an amino or alkylamino group include acetyl, benzoyl, ethoxycarbonyl or benzyl groups.

The reaction of step (c) is conveniently carried out in a solvent or mixture of solvents such as

methylformamide, dimethylformamide, dimethylsulphoxide, benzene, chlorobenzene, tetrahydrofuran, benzene/-tetrahydrofuran or dioxan and may be carried out in the presence of an acid binding agent, e.g. an alkoxide such as potassium tert.butoxide, an alkali metal hydroxide such as sodium or potassium hydroxide, an alkali metal carbonate such as potassium carbonate, an alkali metal amide such as sodium amide or an alkali metal hydride such as sodium hydride, conveniently at temperatures of between 0 and 150°C, preferably at temperatures of between 0 and 50°C.

The optional subsequent splitting off of any protecting group used in step (c) is preferably carried out hydrolytically in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxan/water, in the presence of an acid such as hydrochloric or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide, conveniently at temperatures of between 0 and 100°C, preferably at the boiling temperature of the reaction mixture. However, a benzyl group is preferably split off by hydrogenolysis, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal, conveniently in a solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid, at temperatures of between 0 and 50°C, but preferably at ambient temperature, under a hydrogen pressure of from 1 to 7 bar, preferably from 3 to 5 bar.

In the reaction of step (c) any benzyloxy group present may be converted into the corresponding hydroxy group.

The reaction of step (d) may be carried out with a sulphurising agent such as for example phosphorus pentasulphide or 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetan-2,4-disulfide, conveniently in a solvent such as toluene or xylene at temperatures of between 50 and 150°C, e.g. at the boiling temperature of the reaction mixture.

The reaction of step (e) may conveniently be carried out in the presence of a suitable reducing agent such as a metal hydride, e.g. sodium borohydride, in a suitable solvent such as water/methanol or methanol/ether, at temperatures of between 0 and 80°C, but preferably at temperatures of between 15 and 40°C.

The reduction of step (f) is preferably carried out with a metal hydride such as lithium aluminium hydride or diborane or with a complex of borane and a thioether, e.g. with a borane-dimethylsulfide complex, convenienly in a suitable solvent such as diethyl ether or tetrahydrofuran at temperatures between 0 and 50°C, preferably between 0 and 25°C but more preferably at temperatures of between 10 and 25°C.

The oxidation of step (g) is preferably carried out with an oxidizing agent such as potassium permanganate, selenium dioxide or sodium dichromate, conveniently in a suitable solvent or mixture of solvents such as water, water/dioxan, glacial acetic acid, water/glacial acetic acid or acetic anhydride, at temperatures of between 0 and 100°C, preferably at temperatures of between 20 and 80°C.

The hydrogenation of step (h) may conveniently be carried out in a solvent or mixture of solvents such as methanol, ethanol, ethyl acetate or glacial acetic acid with catalytically activated hydrogen, e.g. with hydrogen in the presence of platinum or palladium/charcoal, under a hydrogen pressure of from 1 to 7 bar, but preferably from 3 to 5 bar, and at temperatures of between 0 and 75°C, preferably at temperatures of between 20 and 50°C.

If a compound of formula XI contains a benzyloxy group, this may be reduced to the corresponding hydroxy group in the reaction of step (h).

If, according to the invention, a compound of formula I wherein R_1 and/or R_3 represents a nitro group is obtained, this can be converted by reduction into a corresponding amino compound of formula I, and if a compound of formula I is obtained wherein R_4 represents a hydroxy or amino group, this may be converted by acylation into a corresponding alkanesulphonyloxy or alkanoylamino compound of formula I.

The subsequent reduction of the nitro compound of step (i) is preferably carried out in a solvent such as water, water/ethanol, methanol, glacial acetic acid, ethyl acetate or dimethylformamide, conveniently with hydrogen in the presence of a hydrogenation catalyst such as Raney nickel, platinum or palladium/charcoal, with metals such as iron, tin or zinc in the presence of an acid, with salts such as iron(II)sulphate, tin(II) chloride or sodium dithionite or with hydrazine in the presence of Raney nickel at temperatures of between 0 and 50°C, but preferably at ambient temperature.

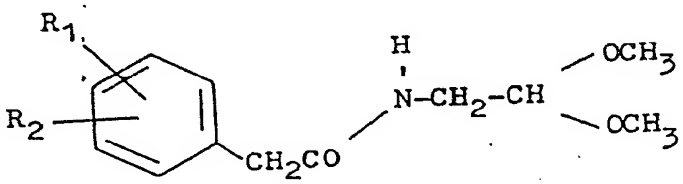
The subsequent acylation of step (i) is conveniently carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetonitrile or dimethylformamide, preferably with a reactive derivative of the acid, for example with methanesulphonic acid chloride, ethanesulphonic acid chloride, n-propanesulphonic acid chloride, acetyl chloride, acetic anhydride or propionic anhydride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine or pyridine, which may simultaneously serve as solvent, at temperatures of between -25°C and 100°C, but preferably at temperatures of between -10°C and the boiling temperature of the solvent used.

Since they have at least one chiral centre, the compounds of formula I obtained may be resolved by conventional methods into their diastereomers, for example by column chromatography, and into their enantiomers, for example by column chromatography on a chiral phase or by crystallisation with optically active acids, e.g. with D- or L-monomethyl tartaric acid, D- or L-diacetyl tartaric acid, D- or L-tartaric acid, D- or L-lactic acid or D- or L-camphoric acid.

The compounds of formula I obtained may also be converted into the acid addition salts thereof, particularly for pharmaceutical use into the physiologically acceptable acid addition salts thereof with inorganic or organic acids. Suitable acids include, for example, hydrochloric, hydrobromic, sulphuric, phosphoric, acetic, lactic, citric, tartaric, succinic, maleic and fumaric acids.

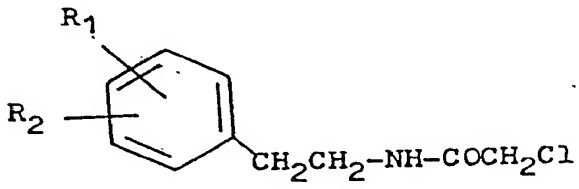
The compounds of formulae II to XI used as starting materials are known from the literature in some cases or may be obtained using methods known per se.

Thus, for example, a starting compound of formula II may be obtained by reacting a corresponding benzazepine with a corresponding halogen compound and optionally by subsequently reacting with a corresponding amine. The corresponding benzazepine of formula V unsubstituted in the 3-position which is required for this may be obtained by cyclising a corresponding compound, e.g. by cyclising a compound of formula XII



(XII)

or a compound of formula XIII



(XIII)

optionally followed by catalytic hydrogenation and/or reduction of the carbonyl group, for example with sodium borohydride/glacial acetic acid (see EP-A-7,070, EP-A-65,229 and EP-A-109,639) and/or oxidation, e.g. with selenium dioxide.

Compound of formulae IV and VII to XI used as starting materials are preferably obtained by reacting corresponding

halogen compounds with corresponding amines, optionally followed by quaternisation and/or splitting off of protecting groups used to protect hydroxy and/or amino groups.

As already mentioned hereinbefore, the compounds of formula I and the physiologically acceptable acid addition salts thereof with inorganic or organic acids have valuable pharmacological properties, particularly a long-lasting lowering effect on heart rate and the effect of reducing the O_2 requirement of the heart, with only minor side-effects on the central nervous system.

Thus, according to a further aspect of the present invention we provide a pharmaceutical composition comprising a compound of formula I as hereinbefore described or a physiologically acceptable acid addition salt thereof together with at least one pharmaceutical carrier or excipient.

The invention also extends to a commercial package containing, as active pharmaceutical ingredient a compound of the invention, together with instructions for its use in treatment of the human or non-human animal body to combat sinus tachycardia or ischaemic heart disease.

For example, the following compounds

A) 3,[(N-(2,(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one,

B) 3-[(N-(2-(3-methyl-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one,

C) 3-[(N-(3-(4-methoxy-phenyl)-propyl)piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one, and

D) 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

were tested for their biological properties as follows:

Effect on heart rate in rats:

The activity of the test substances on the heart rate was investigated, for each dosage, on 2 rats with an average weight of 250-300 g. The rats were anaesthetised with pentobarbital (50 mg/kg i.p. and 20 mg/kg s.c.). The test substances were injected in aqueous solution into the jugular vein (0.1 ml/100 g).

The blood pressure was measured using a cannula inserted in a carotid artery and the heart rate was recorded from an ECG (second or third derivation) derived with needle electrodes. The heart rate of the animals in the control period was between 350 and 400 beats per minute (b/min).

The following Table shows the values found:

Substance	Dosage [mg/kg]	Lowering of heart rate measured 20 minutes after administration of substance [b/min]
A	5.0	- 208
B	5.0	- 148
C	5.0	- 135
D	5.0	- 125

When administered in therapeutic doses the compounds according to the invention show no toxic side effects of any kind. Thus, when administered intravenously

to mice, even in a high dosage of 20 mg/kg, substances A and D showed no toxic side effects apart from a slight sedation.

In view of their pharmacological properties, the compounds according to the invention are suitable for the treatment of sinus tachycardia of various origins and for the prevention and treatment of ischaemic heart disease.

According a still further aspect of the present invention there is provided a method of treatment the human or non-human animal body to combat sinus tachycardia or ischaemic heart disease comprising the administration to said body of a compound of formula I (as hereinbefore described) or a physiologically acceptable acid addition salt thereof and also the use of a compound of formula I (as hereinbefore described) or a physiologically acceptable acid addition salt thereof for the manufacture of a therapeutic agent for use in a method of treatment of the human or non-human animal body to combat sinus tachycardia or ischaemic heart disease.

The dosage required to achieve this effect is conveniently from 0.01 to 0.2 mg/kg of body weight, preferably from 0.03 to 0.15 mg/kg of body weight, once or twice a day. The compounds of formula I and the physiologically acceptable acid addition salts thereof with inorganic or organic acids may be incorporated, optionally together with other active substances, with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, carboxymethyl-

cellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as tablets, coated tablets, capsules, powders, suspensions, drops, ampoules, syrups or suppositories.

The following Examples are provided to illustrate the invention in a non-limiting manner (percentages and ratios are by weight unless otherwise specified):

Example A

N-Benzyl-3-(hydroxymethyl)-piperidine

A mixture of 40.3 g (0.35 mol) of 3-(hydroxymethyl)-piperidine, 97.4 ml (0.70 mol) of triethylamine and 40.3 ml (0.35 mol) of benzyl chloride is heated to 95°C within 30 minutes and left at this temperature for 2 hours. After cooling, the reaction mixture is dissolved in a mixture of 2 molar sodium hydroxide solution and ethyl acetate. The organic phase is washed with water, separated off, dried over magnesium sulphate and concentrated by evaporation in vacuo.
Yield: 57.2 g (79.6% of theory),
Rf value: 0.45 (aluminium oxide neutral, eluant: 3% ethanol in methylene chloride).

Example B

N-Benzyl-3-(bromomethyl)-piperidine

55.1 g (0.268 mol) of N-benzyl-3-(hydroxymethyl)-piperidine are added to 400 ml of 48% hydrobromic acid with vigorous stirring and the mixture is refluxed for 1 hour. Then hydrogen bromide is introduced to saturation point (about 1 hour), the mixture is refluxed for another hour and left to stand overnight. It is then neutralised with solid potassium carbonate whilst cooling with ice and then extracted with methylene chloride. The organic phase is dried over magnesium sulphate and concentrated by evaporation in vacuo.
Yield: 52.0 g (72.2% of theory),
Rf value: 0.85 (aluminium oxide neutral, eluant: methylene chloride).

Example C

3-[(N-Benzyl-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one

17.54 g (0.08 mol) of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one are suspended in 150 ml of dimethylsulphoxide and 8.98 g (0.08 mol) of potassium tert.butoxide are added with stirring. After 45 minutes, 21.45 g (0.08 mol) of N-benzyl-3-(bromomethyl)-piperidine dissolved in 50 ml of dimethylsulphoxide are added dropwise to the resulting solution with stirring. After 2 hours the mixture is poured onto ice water. The aqueous phase is extracted three times, each time with 150 ml of ethyl acetate. The combined organic phases are washed with water, dried over magnesium sulphate, concentrated by evaporation in vacuo and purified over 800 g of aluminium oxide (neutral, activity II-III) with methylene chloride and then with increasing amounts of ethanol (up to 3%).
Yield: 14.3 g (44% of theory),
Rf value: 0.35 (aluminium oxide neutral, eluant: 1% ethanol in methylene chloride).

Example D

3-[(Piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

14.3 g (0.0352 mol) of 3-[(N-benzyl-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one are hydrogenated in 120 ml of glacial acetic acid in the presence of 1.5 g of 10% palladium/charcoal for 4 hours at 50°C under 5 bar of hydrogen. The catalyst is then removed by suction filtering, the glacial acetic acid is distilled off in vacuo

and, after the addition of water, the residue is neutralised with potassium carbonate. The greasy precipitate is extracted with methylene chloride, the organic phase is dried over magnesium sulphate and concentrated by evaporation in vacuo.
Yield: 9.3 g (83% of theory),
Melting point: 152-156°C.

Example E

3-[(Pyridin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one

2.2 g (0.01 mol) of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one are suspended in 10 ml of dimethylsulphoxide and 1.12 g (0.01 mol) of potassium tert.butoxide are added with stirring. After 60 minutes, 1.3 g (0.01 mol) of 3-picolylchloride dissolved in 10 ml of dimethylsulphoxide are added dropwise to the resulting solution with stirring. After 1 hour it is poured onto ice water. The aqueous phase is extracted twice with ethyl acetate. The combined organic phases are washed with water, dried over magnesium sulphate, concentrated by evaporation in vacuo and purified over 200 g of aluminium oxide (neutral, activity II-III) with methylene chloride and then with increasing quantities of methanol (up to 0.8%).
Yield: 1.4 g (45.2% of theory),
Melting point: 144-146°C.

Example F

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-pyridinium-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one bromide

A mixture of 1.1 g (0.0035 mol) of 3-[(pyridin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one and 2-(3,4-dimethoxyphenyl)-ethyl bromide is heated to 110°C for 6 hours. After cooling, the reaction mixture is dissolved in a little methanol/methylene chloride and added dropwise to 200 ml of diethylether, with vigorous stirring. The precipitate obtained is suction filtered and dried.
Yield: 1.6 g (80% of theory),
Melting point: 147-150°C.

Example G

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-(hydroxymethyl)-piperidine

A mixture of 2.30 g (0.02 mol) of 3-(hydroxymethyl)-piperidine, 5.5 ml (0.04 mol) of triethylamine and 4.90 g (0.02 mol) of 2-(3,4-dimethoxy-phenyl)-ethyl bromide is refluxed for 2 hours. After cooling, the reaction mixture is dissolved in a mixture of 2 molar sodium hydroxide solution and methylene chloride. The organic phase is washed with water, separated off, dried over magnesium sulphate, evaporated down in vacuo and purified over 300 g of aluminium oxide (neutral, activity II-III) with methylene chloride and then with increasing amounts of ethanol (up to 2%).
Yield: 4.4 g (78.7% of theory),
Melting point: 87.5-89°C.

Example H

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-(bromomethyl)-piperidine

4.4 g (0.0157 mol) of N-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-(hydroxymethyl)-piperidine are dissolved in 70 ml of carbon tetrachloride and cooled to 0°C. Then 1.63 ml (0.0173 mol) of phosphorus tribromide is added, whereupon a bulky precipitate is immediately formed. The mixture is stirred for 15 hours at ambient temperature, water is added and the mixture is neutralised with 2 molar sodium hydroxide solution. The organic phase is separated off, washed with water, dried over magnesium sulphate, concentrated by evaporation in vacuo and purified over 310 g of aluminium oxide (neutral, activity II-III) with methylene chloride and then with increasing amounts of ethanol (up to 5%).
Yield: 2.0 g (37.2% of theory),
Rf value: 0.5 (aluminium oxide neutral, eluant: 2% ethanol in methylene chloride).

Example I

N-Benzyl-caprolactam

33.9 g (0.3 mol) of caprolactam are dissolved in 200 ml of absolute dimethylsulphoxide and 100 ml of absolute tetramethyl urea and 14.4 g (0.33 mol) of 55% sodium hydride/oil dispersion is added in batches. The resulting jelly-like precipitate is stirred for 2 hours at ambient temperature. Then 38 g = 34.4 ml (0.3 mol) of benzyl chloride are added dropwise, the mixture is stirred for 2 hours at ambient temperature and then poured

onto ice water. The aqueous phase is extracted twice with ethyl acetate. The organic phases are combined, washed four times with water, dried over magnesium sulphate and concentrated by evaporation in vacuo. The residue remaining is distilled in vacuo.

Yield: 49.9 g (81.8% of theory),

$Bp_{0.27\ mm\ Hg}$: 110-114°C.

Example K

1-Benzyl-caprolactam-3-carboxylic acid

180 ml of 1.6 molar butyl lithium solution in n-hexane are added at -60°C to 33.9 g = 47.1 ml (0.33 mol) of diisopropylamine in 450 ml of absolute ether, with stirring and under nitrogen. Then, whilst cooling is continued, 48.8 g (0.24 mol) of N-benzyl-caprolactam dissolved in 150 ml of absolute ether are added dropwise thereto. After the mixture has been stirred for 10 minutes the cooling bath is taken away and carbon dioxide is bubbled in for 15 minutes. The reaction mixture is poured onto ice, the ethereal phase is separated off and extracted twice with 2 molar sodium hydroxide solution. The aqueous/alcoholic phases are combined, extracted with ether, acidified with concentrated hydrochloric acid and extracted twice with methylene chloride. The combined methylene chloride phases are dried over magnesium sulphate and the solvent is distilled off in vacuo.

Yield: 15.7 g (26.5% of theory),

IR spectrum (methylene chloride): 1735 and 1600 cm^{-1} (CO).

Example L

1-Benzyl-3-hydroxymethyl-hexahydro-azepine

14.8 g (0.06 mol) of 1-benzyl-caprolactam-3-carboxylic acid dissolved in 300 ml of absolute tetrahydrofuran are added dropwise to 6.84 g (0.18 mol) of lithium aluminium hydride in 300 ml of absolute tetrahydrofuran. The mixture is then refluxed for 6 hours, then 6.8 ml of water, 6.8 ml of 2-molar sodium hydroxide solution and 21 ml of water are added, whilst cooling with ice water. The precipitate is removed by suction filtering, washed with tetrahydrofuran and the filtrate is concentrated by evaporation in vacuo. The residue is purified by column chromatography over aluminium oxide N (activity II, eluant: methylene chloride).
Yield: 8.4 g (63.8% of theory),
IR spectrum (methylene chloride): 3620 cm^{-1} (OH)

Example M

1-Benzyl-3-bromomethyl-hexahydro-azepine

8.3 g (0.038 mol) of 1-benzyl-3-hydroxymethyl-hexahydro-azepine are dissolved in 200 ml of carbon tetrachloride and 16 ml of phosphorus tribromide are added. The mixture is stirred for 6 hours at ambient temperature, water is then added whilst the mixture is cooled with ice and it is made slightly alkaline with 2-molar sodium hydroxide solution. The aqueous solution is separated off and extracted twice with methylene chloride. The organic phases are combined, dried over magnesium sulphate and concentrated by evaporation in vacuo.
Yield: 8.9 g (82% of theory).

Example N

3-[(N-Benzyl-hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one

2.3 g (0.02 mol) of potassium tert.butoxide are added to a solution of 4.4 g (0.02 mol) of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one in 100 ml of absolute dimethylsulphoxide. After stirring for 30 minutes at ambient temperature, 5.6 g (0.020 mol) of 1-benzyl-3-bromomethyl-hexahydro-azepine are added and the resulting mixture is stirred for 2 hours at ambient temperature. The reaction mixture is dissolved in ethyl acetate and extracted several times with water. The organic phase is dried over magnesium sulphate and evaporated down in vacuo. The residue is purified by column chromatography over aluminium oxide N (activity II, eluant: methylene chloride, methylene chloride + 0.3% ethanol).
Yield: 4.2 g (50% of theory),
IR spectrum (methylene chloride): 1655 cm^{-1} (CO)

Example O

3-[(Hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

4.2 g (0.01 mol) of 3-[(N-benzyl-hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one are hydrogenated in 100 ml of glacial acetic acid in the presence of 0.5 g of 10% palladium/charcoal for 14 hours at 50 psi (0.34 MPa) and at 50°C. The catalyst is removed by suction filtering and the glacial acetic acid is distilled off in vacuo. The residue is taken up in water, made alkaline with 2-molar sodium hydroxide solution and extracted several times with methylene chloride. The organic extract
is dried over magnesium sulphate and concentrated by evaporation in vacuo. Purification by column

chromatography is carried out over aluminium oxide N (activity II, eluant: methylene chloride + 1% ethanol).
Yield: 2.6 g (78.2% of theory),
IR spectrum (methylene chloride): 1650 cm^{-1} (CO).

Example P

7-Carbethoxymethyl-caprolactam

At 0°C 9.2 g = 9 ml (0.05 mol) of ethyl cyclohexanone-2-acetate are added dropwise to 50 ml of concentrated sulphuric acid. Then 3.25 g (0.05 mol) of sodium azide are added in batches. After stirring for 10 hours at 0°C the reaction mixture is poured onto ice water and neutralised with concentrated ammonia with further cooling. After the solution has been saturated with sodium chloride it is extracted several times with n-butanol to which 10% methylene chloride is added. The extract is evaporated down in vacuo and the residue is separated by column chromatography over aluminium oxide N (activity II, eluant: methylene chloride + 0.5% ethanol).
Yield: 5.7 g (56.6% of theory),
Melting point: 108-109°C.

Example Q

2-(2-Hydroxyethyl)-hexahydro-azepine-hydrochloride

5.6 g (0.028 mol) of 7-carbethoxymethyl-caprolactam dissolved in 50 ml of absolute dioxan are added dropwise to 2.6 g (0.06 mol) of lithium aluminium hydride in 100 ml of absolute dioxan, with stirring and refluxing. The mixture is refluxed for 18 hours and then whilst it is cooled with ice water, 2.3 ml of water, 2.3 ml of 15% sodium hydroxide

solution and 6.9 ml of water are added. The precipitate is removed by suction filtering and washed with ether. The filtrate is concentrated by evaporation in vacuo, the residue is dissolved in ether and precipitated with ethereal hydrochloric acid.
Yield: 3 g (59.6% of theory),
Melting point: 75°C.

Example R

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2-(2-hydroxyethyl)-hexahydro-azepine

2.9 g (0.016 mol) of 2-(2-hydroxyethyl)-hexahydro-azepine-hydrochloride are liberated with concentrated sodium hydroxide solution, taken up in methylene chloride and, after drying, evaporated down over magnesium sulphate. The residue is refluxed for 2 hours with 3.9 g (0.016 mol) of 2-(3,4-dimethoxy-phenyl)-ethylbromide in 10 ml of triethylamine. After cooling, the reaction mixture is combined with 2 molar sodium hydroxide solution/methylene chloride. The alkaline phase is separated off and extracted twice with methylene chloride and the combined organic phases are dried over magnesium sulphate. The solvent is distilled off in vacuo and the residue is purified by column chromatography over aluminium oxide N (activity II, eluant: methylene chloride).
Yield: 3.7 g (75.2% of theory).

Example S

2-(2-Bromoethyl)-1-[2-(3,4-dimethoxy-phenyl)-ethyl]-hexahydro-azepine

4 ml of phosphorus tribromide are added dropwise to 2.9 g (9.4 mmol) of N-[2-(3,4-dimethoxy-phenyl)-ethyl]-2-(2-hydroxyethyl)-hexahydro-azepine in 100 ml of carbon tetrachloride, whilst cooling with ice, and the mixture is stirred for 15 hours at ambient temperature. Then water is added, whilst cooling with ice water is continued, and the mixture is made slightly alkaline with 2 molar sodium hydroxide solution. The aqueous/alkaline solution is separated off and extracted twice with methylene chloride. The combined organic solutions are dried over magnesium sulphate and concentrated by evaporation in vacuo.
Yield: 3.6 g (100% of theory).

Example T

3-[(Pyridin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one

a) (Pyridin-3-yl)-methylamino-N-acetaldehyde-dimethyl acetal

5.36 g (0.050 mol) of pyridine-3-aldehyde and 5.26 g (0.050 mol) of aminoacetaldehyde-dimethylacetal are hydrogenated in 80 ml of ethanol in the presence of 0.8 g of 10% palladium/activated charcoal for 2 hours at 20°C under 5 bar (0.5 MPa). The catalyst is then removed by suction filtering and the ethanol is distilled off in vacuo.
Yield: 9.4 g (96% of theory),
Rf value: 0.25 (aluminium oxide, eluant: 2% ethanol in methylene chloride).

b) 3,4-Dimethoxy-phenylacetic acid-N-(acetaldehyde-dimethyl-acetal)-N-[(pyridin-3-yl)-methyl])-amide

7.85 g (0.040 mol) of (pyridin-3-yl)-methylamino-N-acetaldehyde-dimethylacetal and 4.4 g (0.044 mol) of triethylamine are dissolved in 50 ml of methylene chloride. Whilst cooling with ice, 8.58 g (0.040 mol) of 3,4-dimethoxy-phenylacetic acid chloride are added dropwise to this mixture and the resulting mixture is stirred for 1 hour at 20°C. It is then extracted 3 times with water and the organic phase is dried over magnesium sulphate and then concentrated by evaporation.
Yield: 12.6 g (84% of theory)
Rf value: 0.5 (on silica gel, eluant: 5% ethanol in methylene chloride).

c) 3-[(Pyridin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one

3.74 g (0.010 mol) of 3,4-dimethoxy-phenylacetic acid-N-(acetaldehyde-dimethylacetal)-N-[(pyridin-3-yl)-methyl]-amide are dissolved in 10 ml of concentrated hydrochloric acid and 10 ml of glacial acetic acid and stirred for 60 hours at 20°C. The mixture is then poured onto ice water, neutralised with 25% sodium hydroxide solution and extracted twice with methylene chloride. The organic phase is dried over magnesium sulphate, filtered off and concentrated by rotation.
Yield: 1.85 g (60% of theory),
Melting point: 144-146°C (from acetone).

Example U

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-tosyloxymethyl-pyrrolidine

a) N-Benzyl-2-pyrrolidone

14.4 g (0.33 mol) of 50% sodium hydride dispersion in oil are added in batches to 25.5 g (0.3 mol) of 2-pyrrolidone in 300 ml of absolute dimethylsulphoxide. The mixture is then stirred for 5 hours at 40 to 50°C and at 25-30°C 56.4 g = 39.2 ml (0.33 mol) of benzyl bromide are added dropwise. After stirring for 10 hours at ambient temperature the reaction mixture is dissolved in 500 ml of ethyl acetate and extracted several times with water. The organic phase is separated off, dried over magnesium sulphate and the solvent is eliminated in vacuo. The residue obtained is purified over 900 g of aluminium oxide (neutral, activity II) with methylene chloride and 0.1% ethanol.
Yield: 35.6 g (67.7% of theory),
Rf value: 0.77 (aluminium oxide, neutral, eluant: 5% ethanol in methylene chloride).

b) N-Benzyl-2-pyrrolidone-3-carboxylic acid

At -60°C, 150 ml of 1.6 molar butyl lithium solution in n-hexane are added to 28.3 g = 39.3 ml (0.28 mol) of diisopropylamine in 400 ml of absolute ether, with stirring and under nitrogen. 35.1 g (0.2 mol) of N-benzyl-2-pyrrolidone dissolved in 150 ml of absolute ether are added dropwise thereto at -60°C. The cooling bath is taken away and dry carbon dioxide is introduced for 15 minutes. After stirring for 10 minutes the mixture is poured onto ice, the organic phase is separated off and extracted twice with 2 molar sodium hydroxide solution. The combined aqueous phases are extracted once with ether and then acidified with concentrated hydrochloric acid, with cooling. The aqueous phase is extracted twice with methylene chloride and, after the organic phase has been dried over magnesium sulphate, it is concentrated by evaporation in vacuo.

Yield: 35 g (79.8% of theory),
Rf value: 0.42 (silica gel, eluant: 5% ethanol in methylene chloride).

c) N-Benzyl-3-hydroxymethyl-pyrrolidine

35 g (0.16 mol) of N-benzyl-2-pyrrolidone-3-carboxylic acid dissolved in 250 ml of absolute tetrahydrofuran is added dropwise, with stirring, to 12.2 g (0.32 mol) of lithium aluminium hydride in 350 ml of absolute tetrahydrofuran. After refluxing for 6 hours, 18.2 ml of water, 12.2 ml of 15% sodium hydroxide solution and 36.6 ml of water are added, whilst cooling with ice water. The precipitate formed is suction filtered and washed with tetrahydrofuran. The combined filtrates are concentrated by evaporation in vacuo and the residue obtained is purified over 900 g of aluminium oxide (neutral, activity II) with methylene chloride and then with increasing amounts of ethanol (up to 2%).
Yield: 16 g (52.3% of theory),
Rf value: 0.42 (aluminium oxide, neutral, eluant: 5% ethanol in methylene chloride).

d) 3-Hydroxymethyl-pyrrolidine

14 g (0.073 mol) of N-benzyl-3-hydroxymethyl-pyrrolidine are hydrogenated for 7 hours at 50°C and at 5 bar (0.5 MPa) in 300 ml of methanol and in the presence of 1.5 g of 20% palladium hydroxide/activated charcoal. The catalyst is then removed by suction filtering and the filtrate is concentrated by evaporation in vacuo.
Yield: 7.3 g (99% of theory),
Mass spectrum: molecular peak 101

e) N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-hydroxymethyl-pyrrolidine

3 g (0.03 mol) of 3-hydroxymethyl-pyrrolidine and 7.5 g of 2-(3,4-dimethoxy-phenyl)-ethylbromide are heated in 20 ml of triethylamine for 7 hours at 100°C. The excess triethylamine is then distilled off in vacuo and the residue obtained is dissolved in methylene chloride and 6 molar sodium hydroxide solution. The organic phase is separated off, dried over magnesium sulphate and concentrated by evaporation in vacuo. The residue obtained is then purified over 400 g of alumium oxide (neutral, activity II) with methylene chloride and with increasing amounts of ethanol (up to 1%).
Yield: 5.4 g (67.8% of theory),
Rf value: 0.41 (aluminium oxide, neutral, eluant: 5% ethanol in methylene chloride).

f) N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-tosyloxymethyl-pyrrolidine

1.3 g (0.005 mol) of N-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-hydroxymethyl-pyrrolidine are dissolved in 10 ml of pyridine, 1.05 g (0.0055 mol) of p-toluenesulphonic acid chloride are added and the mixture is stirred for 6 hours at ambient temperature. The excess pyridine is then distilled off in vacuo, the residue obtained is dissolved in methylene chloride and the organic phase is extracted with ice water. After the organic phase has been dried over magnesium sulphate it is concentrated by evaporation in vacuo.
Yield: 1.4 g (66.7% of theory),
Rf value: 0.40 (aluminium oxide, neutral, eluant: 2% ethanol in methylene chloride).

Example 1

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

A mixture of 6.37 g (0.020 mol) of 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one, 5.6 ml (0.040 mol) of triethylamine and 4.90 g (0.020 mol) of 2-(3,4-dimethoxy-phenyl)-ethyl bromide is refluxed for 2 hours. The initial suspension changes into a clear solution and after about 30 minutes begins to precipitate in a jelly-like form. After cooling, the reaction mixture is dissolved in a mixture of 2 molar sodium hydroxide solution and methylene chloride. The organic phase is separated off, washed with water, dried over magnesium sulphate, evaporated down in vacuo and purified over 800 g of aluminium oxide (neutral, activity II-III) with methylene chloride and then with increasing quantities of ethanol (up to 2%). The hydrochloride is precipitated from a solution in acetone with methanolic hydrochloric acid.
Yield: 6.2 g (59.7% of theory),
Melting point: 218-219°C

Calculated:	C	64.79	H	7.57	N 5.40
Found:		64.88		7.55	5.21

Example 2

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrobromide

3.7 g (0.0067 mol) of 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-pyridinium-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one-bromide are hydrogenated

in 70 ml of methanol in the presence of 0.7 g of platinum dioxide for 3 hours at ambient temperature and under 5 bar (0.5 MPa). The catalyst is removed by suction filtering, the methanol is distilled off in vacuo and the residue is dissolved in a little methanol and mixed with acetone. The precipitate is suction filtered and dried.

Yield: 2.7 g (71.4% of theory),

Melting point: 225-227°C

Calculated:	C	59.68	H	6.98	N 4.97
Found:		59.45		7.10	5.00

Example 3

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one-hydrochloride

1.01 g (0.005 mol) of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one are suspended in 10 ml of dimethylsulphoxide and 0.56 g (0.005 mol) of potassium tert.butoxide are added with stirring. After 45 minutes, 1.7 g (0.005 mol) of N-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-(bromomethyl)-piperidine dissolved in 5 ml of dimethylsulphoxide are added dropwise to the resulting solution with stirring. After 40 minutes it is poured onto ice water. The aqueous phase is extracted three times with ethyl acetate. The combined organic phases are washed with water, dried over magnesium sulphate, concentrated by evaporation in vacuo and purified over 200 g of aluminium oxide (neutral, activity II-III) with methylene chloride and then with increasing amounts of ethanol (up to 0.5%). The hydrochloride is precipitated from a solution in acetone using methanolic hydrochloric acid.

Yield: 0.62 g (23.9% of theory),

Melting point: 117-121°C
Calculated: C 65.04 H 7.21 N 5.42
Found: 64.86 7.18 5.35

Example 4

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine-dihydrochloride

A solution of 0.96 g (0.002 mol) of 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one in 20 ml of tetrahydrofuran is added dropwise, under a nitrogen atmosphere, to a solution of 0.24 ml (0.002 mol) of boron trifluoride etherate and 0.3 ml (0.003 mol) of borane dimethylsulphide complex (10 molar solution in toluene) and the resulting mixture is then refluxed for 3 hours. After the reaction mixture has cooled, methanol is added dropwise thereto. Then 2 ml of methanolic hydrochloric acid are added and the mixture is refluxed for 2 hours. The methanol and tetrahydrofuran are distilled off and the residue is mixed with water and then neutralised with 2 molar sodium hydroxide solution. The greasy precipitate is extracted with methylene chloride. The organic phase is dried over magnesium sulphate, concentrated by evaporation in vacuo and purified over 50 g of aluminium oxide (neutral, activity II-III) with methylene chloride and then with increasing amounts of ethanol (up to 0.5%). The dihydrochloride is precipitated from a solution in acetone using methanolic hydrochloric acid.
Yield: 0.28 g (27.7% of theory),
Melting point: 238-240°C
Calculated: C 62.09 H 7.81 N 5.17

Found:	61.88	7.84	5.42

Example 5

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-thione-hydrochloride

1.4 g (0.0029 mol) of 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 0.41 g (0.0018 mol) of phosphorus pentasulphide are heated to 100°C in 20 ml of pyridine for 3 hours. After concentration in vacuo the residue obtained is purified over 120 g of aluminium oxide (neutral, activity II-III) with ethyl acetate/cyclohexane (80/20). The hydrochloride is precipitated from a solution in acetone with methanolic hydrochloric acid.

Yield: 0.47 g (30.3% of theory),

Melting point: 206-207°C

Calculated:	C	62.84	H	7.35	N	5.24	S 5.99
Found:		62.54		7.43		5.35	6.15

Example 6

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-1,2-dione

3.8 g (0.0079 mol) of 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one are added at 70°C to a suspension of 1.4 g (0.0128 mol) of selenium dioxide and 0.8 g of kieselguhr in dioxan/water and refluxed for 16 hours. After cooling, the mixture is diluted with a little ethanol and suction filtered. The filtrate is evaporated down in vacuo

and purified over 310 g of aluminium oxide (neutral, activity II-III) with methylene chloride and increasing amounts of ethanol (up to 1%).
Yield: 2.15 g (54.8% of theory),
Melting point: 130-132°C

Calculated:	C	67.72	H	7.31	N 5.64
Found:		67.53		7.14	5.65

Example 7

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1-hydroxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

0.70 g (0.0014 mol) of 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-1,2-dione are dissolved in a mixture of methanol and water (95:5), 0.060 g (0.0016 mol) of sodium borohydride are added and the mixture is stirred for 20 minutes at ambient temperature. Then it is acidified with 2 molar hydrochloric acid, neutralised with ammonia and extracted with methylene chloride. The organic phase is dried over magnesium sulphate, concentrated by evaporation in vacuo and the residue obtained is purified over 100 g of aluminium oxide (neutral, activity II-III) with methylene chloride and then with increasing amounts of ethanol (up to 15%). The hydrochloride is precipitated from a solution in acetone using methanolic hydrochloric acid.
Yield: 0.47 g (62.3% of theory),
Melting point: 118-124°C

Calculated:	C	62.85	H	7.35	N 5.24
Found:		62.60		7.39	5.30

Example 8

3-[(N-(2-(4-Amino-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-dihydrochloride

1.7 g (0.0036 mol) of 3-[(N-(2-(4-nitro-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one are hydrogenated in 40 ml of methanol in the presence of 0.3 g of 10% palladium/charcoal for 2 hours at ambient temperature and under 5 bar (0.5MPa) of hydrogen. Then the catalyst is removed by suction filtering and the methanol is distilled off in vacuo. The hydrochloride is precipitated from a solution of the residue in acetone using methanolic hydrochloric acid.
Yield: 1.1 g (59.8% of theory),
Melting point: 236-240°C

Calculated:	C	61.17	H	7.31	N 8.23
Found:		60.85		7.63	8.12

Example 9

3-[(N-(2-(4-Acetamino-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

0.88 g (0.002 mol) of 3-[(N-(2-(4-amino-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 0.3 ml (0.0022 mol) of triethylamine are dissolved in 10 ml of methylene chloride and 0.16 ml (0.0022 mol) of acetyl chloride are added dropwise with stirring. After 30 minutes water is added. The aqueous phase is extracted three times with methylene chloride. The organic phase is dried over magnesium sulphate and evaporated down in vacuo. The hydrochloride is precipitated from a solution of the residue in acetone using methanolic hydrochloric acid.

Yield: 0.61 g (59.1% of theory),
Melting point: 187-192°C

Calculated:	C	65.16	H	7.42	N	8.14
Found:		64.95		7.45		7.94

Example 10

3-[(N-(3-(4-Amino-3,5-dibromo-phenoxy)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 3-(4-amino-3,5-dibromo-phenoxy)-propyl chloride analogously to Example 1.
Yield: 20.4% of theory,
Melting point: > 95°C (decomp.)

Calculated:	C	49.00	H	5.48	N	6.35	Br	24.15
Found:		49.12		5.80		5.83		24.00

Example 11

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(3,4-dimethoxy-phenyl)-ethylbromide analogously to Example 1.
Yield: 31.7% of theory,
Melting point: 142-143°C

Calculated:	C	64.47	H	7.01	N	5.57
Found:		64.36		7.17		5.42

Example 12

3-[(N-(3,4-Dimethoxy-benzyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 3,4-dimethoxy-benzyl chloride analogously to Example 1.
Yield: 30.7% of theory,
Melting point: 135°C (decomp.)

Calculated:	C	63.68	H	6.80	N 5.73
Found:		63.45		7.02	5.41

Example 13

3-[(N-(2-Phenylethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-phenylethylbromide analogously to Example 1.
Yield: 43.5% of theory,
Melting point: 241-243°C

Calculated:	C	68.03	H	7.69	N 6.10
Found:		67.89		7.89	6.36

Example 14

3-[(N-(2-(3-Nitro-4-acetamino-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(3-nitro-4-acetamino-phenyl)-ethyl bromide analogously to Example 1.

Yield: 22.3% of theory,
Melting point: > 173°C (decomp.)

Calculated:	C	59.94	H	6.65	N 9.99
Found:		59.92		6.77	9.98

Example 15

3-[(N-(2-(3,4,5-Trimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(3,4,5-trimethoxy-phenyl)-ethyl bromide analogously to Example 1.
Yield: 22.6% of theory,
Melting point: 135-137°C

Calculated:	C	63.53	H	7.53	N 5.10
Found:		63.50		7.82	5.09

Example 16

3-[(N-(3-(4-Methoxy-phenyl)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 3-(4-methoxyphenyl)-propyl bromide analogously to Example 1.
Yield: 29.4% of theory
Melting point: 215-218°C

Calculated:	C	66.85	H	7.81	N 5.57
Found:		66.67		7.65	5.53

Example 17

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-2,3-dihydro-1H-benzazepine

A suspension of 0.06 g (0.0016 mol) of lithium aluminium hydride in 20 ml of absolute tetrahydrofuran is mixed with 0.31 g (0.00065 mol) of 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one and then stirred for 1 hour at ambient temperature. 10% ammonium chloride solution is added, whilst cooling with ice water, and the precipitate formed is suction filtered. The filtrate is concentrated by evaporation in vacuo and the residue is purified over 30 g of aluminium oxide (neutral, activity II-III) with methylene chloride.
Yield: 0.05 g (16.5% of theory),
Rf value: 0.5 (aluminium oxide, eluant: 2% ethanol in methylene chloride)

Calculated:	C	72.07	H	8.21	N 6.00
Found:		71.90		8.39	5.89

Example 18

3-[(N-(2-(4-Methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(4-methoxy-phenyl)-ethylbromide analogously to Example 1.
Yield: 19.8% of theory,
Melting point: 227-230°C

Calculated:	C	66.31	H	7.63	N 5.73
Found:		66.46		7.57	5.73

Example 19

3-[(N-(2-(4-Nitro-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(4-nitro-phenyl)-ethylbromide analogously to Example 1.
Yield: 66.8% of theory,
Melting point: 239-245°C

Calculated:	C	61.91	H	6.80	N 8.34
Found:		62.25		6.66	8.23

Example 20

3-[(N-(2-(3-Methyl-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(3-methyl-phenyl)-ethylbromide analogously to Example 1.
Yield: 38.1% of theory,
Melting point: 234-237°C

Calculated:	C	68.55	H	7.88	N 5.92
Found:		68.68		7.87	6.14

Example 21

3-[(N-(2-(3-Methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(3-methoxy-phenyl)-ethylbromide analogously to Example 1.
Yield: 23.7% of theory,

Melting point: 199-202°C
Calculated: C 66.31 H 7.63 N 5.73
Found: 66.61 7.59 5.91

Example 22

3-[(N-(2-(4-Methyl-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(4-methyl-phenyl)-ethylbromide analogously to Example 1.
Yield: 34.7% of theory,
Melting point: 233-236°C
Calculated: C 68.55 H 7.88 N 5.92
Found: 68.30 7.89 5.84

Example 23

3-[(N-(3-(4-Bromo-phenyl)-propyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 3-(4-bromophenyl)-propyl bromide analogously to Example 1.
Yield: 34.8% of theory,
Melting point: 100-104°C
Calculated: C 58.75 H 6.57 N 5.08 Br 14.48
Found: 58.40 6.66 4.79 14.21

Example 24

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3-dihydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 7,8-methylenedioxy-1,3-dihydro-2H-3-benzazepin-2-one and N-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-(bromomethyl)-piperidine analogously to Example 3.
Yield: 8.6% of theory,
Melting point: 199-201°C

Calculated:	C	64.73	H	6.64	N 5.59
Found:		64.77		6.55	5.57

Example 25

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(3,4-dimethoxy-phenyl)-ethylbromide analogously to Example 1.
Yield: 23.8% of theory,
Melting point: 113-115°C

Calculated:	C	65.33	H	7.75	N 5.26
Found:		65.11		7.67	5.04

Example 26

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

660 mg (2 mmol) of 3-[(hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 540 mg (2.2 mmol) of 2-(3,4-dimethoxyphenyl)-ethylbromide are refluxed for 1 hour in 3 ml of triethylamine. The reaction mixture is cooled and taken up in methylene chloride and 2-molar sodium hydroxide solution. The alkaline phase

is separated off and extracted twice with methylene chloride. The combined organic phases are dried over magnesium sulphate and evaporated down in vacuo. Purification is carried out by column chromatography over 100 g of aluminium oxide (activity II, eluant: methylene chloride + 0.3% ethanol). The fractions obtained are concentrated by evaporation in vacuo, the residue is dissolved in acetone and the hydrochloride is precipitated using ethereal hydrochloric acid.

Yield: 600 mg (56.3% of theory),
Melting point: 164-165°C

Calculated:	C	65.33	H	7.75	N	5.25
Found:		65.12		7.59		5.22

Example 27

3-[(N-(3-(4-Amino-3,5-dibromo-phenoxy)-propyl)-hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-dihydrochloride

Prepared from 1.2 g (3.6 mmol) of 3-[(hexahydro-azepin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 1.36 g (3.96 mmol) of 3-(4-amino-3,5-dibromo-phenoxy)-propyl chloride in 5 ml triethylamine analogously to Example 26.
Yield: 350 mg (13.7% of theory),
Melting point: 134-136°C

Calculated:	C	47.22	H	5.52	Br	22.42	N 5.36
Found:		47.40		5.86		22.22	5.49

Example 28

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-hexahydro-azepin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one

Prepared from 3.6 g (9.4 mmol) of 2-(2-bromoethyl)-1-[2-(3,4-dimethoxy-phenyl)-ethyl]-hexahydro-azepine and 2.06 g (9.4 mmol) of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one analogously to Example 3.
Yield: 1.3 g (27.2% of theory),
Oil, IR spectrum (methylene chloride): 1655 cm^{-1} (CO)
Calculated: C 70.83 H 7.93 N 5.51
Found: 70.56 7.80 5.27

Example 29

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-hexahydro-azepin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

1.2 g (2.36 mol) of 3-[N-(2-(3,4-dimethoxy-phenyl)-ethyl)-hexahydro-azepin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one are hydrogenated in 80 ml of glacial acetic acid for 4 hours at 45°C and under 5 bar (0.5MPa) in the presence of 1 g of 10% palladium/activated charcoal (10%). The catalyst is removed by suction filtering, the filtrate is concentrated by evaporation in vacuo, the residue is dissolved in 100 ml of methylene chloride and extracted once with 50 ml of 2N sodium hydroxide solution. The organic phase is dried over magnesium sulphate and evaporated down in vacuo. Purification is carried out by column chromatography over 100 g of aluminium oxide (neutral, eluant: methylene chloride + 1% ethanol).
Yield: 200 mg (17% of theory),
Calculated: C 70.56 H 8.29 N 5.49
Found: 70.60 8.34 5.37
IR spectrum (methylene chloride): 1650 cm^{-1} (CO)

Example 30

3-[(N-(2-(3,4-Methylenedioxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(3,4-methylenedioxy-phenyl)-ethylbromide analogously to Example 1.
Yield: 85.7% of theory,
Melting point: 234-235°C

Calculated:	C	66.73	H	6.03	N 5.99
Found:		66.58		6.31	5.94

Example 31

3-[(N-(3,4-dichloro-benzyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidinyl-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 3,4-dichloro-benzyl chloride analogously to Example 1.
Yield: 80% of theory,
Melting point: 240-242°C

Calculated:	C	57.90	H	5.47	N 5.63
Found:		57.77		5.35	5.46

Example 32

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one

0.79 g (3.6 mmol) of 7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one are suspended in 30 ml of absolute dimethylsulphoxide and 160 ml (3.6 mmol)

of 55% sodium hydride dispersion in oil are added. After stirring for 2 hours at ambient temperature and for half an hour at 40°C 1.3 g (3 mmol) of N-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-tosyloxy-methyl-pyrrolidine are added and the resulting mixture is heated for 3 hours to 50 to 55°C. After cooling, the reaction mixture is then dissolved in ethyl acetate and extracted several times with water and then twice with 25% acetic acid. The acid extract obtained is made alkaline with 6 molar sodium hydroxide solution and extracted twice with methylene chloride. After the organic phase has been dried the solvent is eliminated in vacuo and the residue obtained is purified over 100 g of aluminium oxide (neutral, activity II) with methylene chloride and then with increasing amounts of ethanol (up to 2%).
Yield: 270 mg (19.3% of theory),
IR spectrum (methylene chloride): 1655 cm^{-1} (CO)

Calculated:	C	69.50	H	7.35	N 6.00
Found:		69.37		7.38	6.12

Example 33

3-[(N-(2-(3,4-Dimethoxy-phenyl)-ethyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

Prepared from 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-pyrrolidin-3-yl)-methyl]-7,8-dimethoxy-1,3-dihydro-2H-3-benzazepin-2-one analogously to Example 29.
Yield: 21.7% of theory,
IR spectrum (methylene chloride): 1650 cm^{-1} (CO)

Calculated:	C	69.29	H	7.75	N 5.98
Found:		69.20		7.84	5.92

Example 34

3-[(N-(3-(3-Methoxy-phenoxy)-propyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 3-(3-methoxy-phenoxy)-propyl chloride analogously to Example 1.
Yield: 42% of theory,
Melting point: 135-138°C

Calculated:	C	64.46	H	7.01	N 5.57
Found:		64.46		7.02	5.57

Example 35

3-[(N-(3-(3-Methyl-phenoxy)-propyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 3-(3-methyl-phenoxy)-propylchloride analogously to Example 1.
Yield: 34% of theory,
Melting point: 122-124°C

Calculated:	C	65.36	H	7.32	N 5.65
Found:		65.01		7.61	5.64

Example 36

3-[(N-(2-(4-Amino-3,5-dichloro-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(4-amino-3,5-dichloro-phenyl)-ethylbromide analogously to Example 1.

Yield: 60% of theory,
Melting point: 137-140°C
Calculated: C 57.03 H 5.58 N 6.98
Found: 57.27 5.82 6.59

Example 37

3-[(N-(3-(3,4-Methylenedioxy-phenoxy)-propyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 3-(3,4-methylenedioxy-phenoxy)-propyl chloride analogously to Example 1.
Yield: 39.9% of theory,
Melting point: 127-129°C
Calculated: C 62.92 H 6.43 N 5.42
Found: 62.98 6.41 5.05

Example 38

3-[(N-(4-(4-Methoxy-phenyl)-butyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 4-(4-methoxy-phenyl)-butyl bromide analogously to Example 1.
Yield: 42% of theory,
Melting point: 158-163°C
Calculated: C 67.12 H 7.44 N 5.59
Found: 66.98 7.27 5.51

Example 39

3-[(N-(2-(4-Methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(4-methoxy-phenyl)-ethylchloride in dimethylformamide/potassium carbonate at 120°C analogously to Example 1.
Yield: 55.6% of theory,
Melting point: 226-228°C

Calculated:	C	66.02	H	7.03	N 5.92
Found:		66.18		7.03	5.87

Example 40

3-[(N-(2-(Phenoxy)-ethyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-phenoxy-ethylbromide analogously to Example 1.
Yield: 55.7% of theory,
Melting point: 124-127°C

Calculated:	C	64.16	H	6.98	N 6.10
Found:		64.42		7.02	6.14

Example 41

3-[(N-(2-(4-Methoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-

2-one and 2-(4-methoxy-phenyl)-ethylbromide analogously to Example 1.
Yield: 34.6% of theory,
Melting point: 110-115°C

Calculated:	C	66.58	H	7.24	N 5.75
Found:		66.50		7.18	5.70

Example 42

3-[(N-(4-Methoxy-phenyl)-methyl)-piperidin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 4-methoxy-benzylbromide analogously to Example 1.
Yield: 52% of theory,
Melting point: 148-152°C

Calculated:	C	66.02	H	7.03	N 5.92
Found:		65.90		7.10	5.98

Example 43

3-[(N-(3,4-Dimethoxy-phenyl)-methyl)-piperidin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrobromide

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 3,4-dimethoxy-benzylbromide analogously to Example 1.
Yield: 27% of theory,
Melting point: 138-140°C

Calculated:	C	59.23	H	6.42	N 5.11
Found:		59.40		6.49	5.23

Example 44

3-[(N-(2-(4-Nitro-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(4-nitro-phenyl)-ethylbromide analogously to Example 1.
Yield: 22% of theory,
Melting point: 130-132°C

Calculated:	C	62.20	H	6.43	N 8.37
Found:		62.16		6.57	8.32

Example 45

3-[(N-(2-(3-Trifluoromethylphenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(3-trifluoromethyl-phenyl)-ethylbromide analogously to Example 1.
Yield: 32% of theory,
Melting point: from 150°C (decomp.)

Calculated:	C	61.53	H	6.50	N 5.32
Found:		61.70		6.42	5.27

R_f value: 0.36 (silica gel, methylene chloride/methanol = 10/1)

Example 46

3-[(N-(3-(3,5-Dimethoxy-phenoxy)-propyl)-piperidin-3-yl)-methyl]-7,8-methylenedioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-methylene-dioxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 3-(3,5-dimethoxy-phenoxy)-propylchloride analogously to Example 1.
Yield: 46.4% of theory,
Melting point: 102-107°C

Calculated:	C	63.09	H	7.00	N 5.25
Found:		62.96		6.86	5.50

Example 47

3-[(N-(2-Phenyl-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-2H-3-benzazepin-2-one and 2-phenyl-ethylbromide analogously to Example 1.
Yield: 37% of theory,
Melting point: 130-132°C

Calculated:	C	68.55	H	7.88	N 5.92
Found:		68.42		7.97	5.75

Example 48

3-[(N-(3-(4-Methoxy-phenyl)-propyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-2H-3-benzazepin-2-one and 3-(4-methoxyphenyl)-propylbromide analogously to Example 1.
Yield: 43% of theory,
Melting point: 109-112°C

Calculated:	C	67.36	H	7.99	N 5.42
Found:		67.19		7.88	5.38

Example 49

3-[(N-(2-(3-Methyl-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-2H-3-benzazepin-2-one and 2-(3-methylphenyl)-ethylbromide analogously to Example 1.
Yield: 31% of theory,
Melting point: 124-126°C

Calculated:	C	69.04	H	8.07	N 5.75
Found:		68.91		7.69	5.72

Example 50

3-[(N-(2-(4-Methoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-2H-3-benzazepin-2-one and 2-(4-methoxyphenyl)-ethylbromide analogously to Example 1.
Yield: 48% of theory,
Melting point: 112-114°C

Calculated:	C	66.85	H	7.81	N 5.57
Found:		66.69		7.86	5.65

Example 51

3-[(N-(2-(4-Nitro-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-2H-3-benzazepin-2-one and 2-(4-nitrophenyl)-ethylbromide analogously to Example 1.

Yield: 8% of theory,
Melting point: 126-128°C

Calculated:	C	62.59	H	7.00	N 8.11
Found:		62.56		6.91	8.16

Example 52

3-[(N-(2-(4-Methyl-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-2H-3-benzazepin-2-one and 2-(4-methylphenyl)-ethyl-bromide analogously to Example 1.
Yield: 23% of theory,
Melting point: 109-111°C

Calculated:	C	69.04	H	8.07	N 5.75
Found:		68.84		7.90	6.03

Example 53

3-[(N-(2-(3-Methoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-2H-3-benzazepin-2-one and 2-(3-methoxyphenyl)-ethyl-bromide analogously to Example 1.
Yield: 25% of theory,
Melting point: 125-127°C

Calculated:	C	66.85	H	7.81	N 5.57
Found:		65.68		7.67	5.20

Example 54

3-[(N-(2-(3,4,5-Trimethoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-2H-3-benzazepin-2-one and 2-(3,4,5-trimethoxy-phenyl)-ethylbromide analogously to Example 1.
Yield: 15% of theory,
Melting point: 138-140°C

Calculated:	C	63.98	H	7.70	N	4.97
Found:		63.74		7.55		4.65

Example 55

3-[(N-(2-(3-Methoxy-4-methanesulphonyloxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(N-(2-(3-methoxy-4-hydroxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride and methanesulphonic acid chloride analogously to Example 9.
Yield: 66% of theory,
Melting point: 202-204°C

Calculated:	C	57.67	H	6.74	N	4.80	S 5.50
Found:		57.72		6.91		4.87	6.31

Example 56

3-[(N-(2-(3-Methoxy-4-hydroxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

a) 3-[(N-(2-(4-Benzyloxy-3-methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(4-benzyloxy-3-methoxy-phenyl)-ethylbromide analogously to Example 1.

Yield: 56% of theory,
Melting point: 216-217°C
Calculated: C 68.61 H 7.28 N 4.71
Found: 68.80 7.38 4.73

b) 3-[(N-(2-(3-Methoxy-4-hydroxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

Prepared from 3-[(N-(2-(4-benzyloxy-3-methoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one in glacial acetic acid analogously to Example 8.
Yield: 77% of theory,
Melting point: 173-175°C
Calculated: C 69.21 H 7.74 N 5.98
Found: 69.07 7.79 6.06

Example 57

3-[N-(2-(2-Fluorophenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-dihydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(2-fluorophenyl)-ethylbromide analogously to Example 1.
Yield: 49% of theory,
Melting point: from 210°C
Calculated: C 60.82 H 6.87 N 5.46
Found: 60.88 6.73 5.60
R_f value: 0.33 (silica gel, methylene chloride/methanol = 10/1)

Example 58

3-[N-(2-(4-Fluorophenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one-hydrochloride

Prepared from 3-[(piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and 2-(4-fluorophenyl)-ethylbromide analogously to Example 1.
Yield: 56% of theory,
Melting point: 245°C (decomp.)

Calculated:	C	65.47	H	7.18	N 5.87
Found:		65.78		7.25	5.99

R_f value: 0.31 (silica gel, methylene chloride/methanol = 10/1)

Example I

Tablets containing 7.5 mg of 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

Composition:

1 tablet contains:

Active substance	7.5 mg
Corn starch	59.5 mg
Lactose	48.0 mg
Polyvinylpyrrolidone	4.0 mg
Magnesium stearate	1.0 mg
	120.0 mg

Preparation

The active substance, corn starch, lactose and polyvinylpyrrolidone were mixed together and moistened with water. The moist mixture is pushed through a screen with a mesh size of 1.5 mm and dried at about 45°C. The dry granulate is passed through a 1.0 mm mesh screen and mixed with magnesium stearate. The final mixture is compressed in a tablet press with dies 7 mm in diameter provided with a dividing notch to form tablets.
Weight of tablet: 120 mg.

Example II

Coated tablets containing 5 mg of 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

1 tablet core contains:

Active substance	5.0 mg
Corn starch	41.5 mg
Lactose	30.0 mg

Polyvinylpyrrolidone	3.0 mg
Magnesium stearate	0.5 mg
	80.0 mg

Preparation

The active substance, corn starch, lactose and polyvinylpyrrolidone are throughly mixed and moistened with water. The moist mass is forced through a 1 mm screen, dried at about 45°C and then the granulate is passed through the same screen. After magnesium stearate has been added, convex tablet cores with a diameter of 6 mm are compressed in a tablet making machine. The tablet cores thus produced are coated in a conventional manner with a coating consisting essentially of sugar and talc. The finished coated tablets are polished with wax.
Weight of coated tablet: 130 mg.

Example III
Ampoules containing 5 mg of 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

1 ampoule contains:

Active substance	5.0 mg
Sorbitol	50.0 mg
Water for injections ad	2.0 ml

Preparation

In a suitable mixing vessel the active substance is dissolved in water for injections and the solution is made isotonic with sorbitol.

After being filtered through a diaphragm filter the solution is transferred under a current of

N_2 into purified and sterilized ampoules and autoclaved for 20 minutes in a jet of steam.

Example IV

Suppositories containing 10 mg of 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

1 suppository contains:

Active substance	0.010 g
Hard fat (e.g. Witepsol* H 19 and W 45)	1.690 g
	1.700 g

Preparation

The hard fat is melted. At 38°C the ground active substance is homogeneously dispersed in the melt. It is cooled to 35°C and poured into slightly chilled suppository moulds.

Example V

Drops solution containing 10 mg of 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

100 ml of solution contain:

Active substance	0.2 g
Hydroxyethylcellulose	0.15g
Tartaric acid	0.1 g
Sorbitol solution (with 70% dry matter)	30.0 g
Glycerol	10.0 g
Benzoic acid	0.15g
Distilled water ad	100 ml

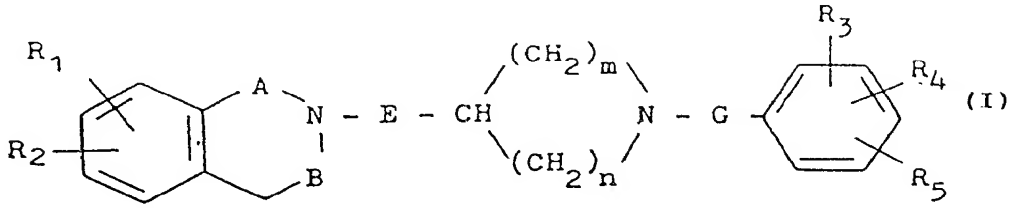
* Trade Mark

Preparation

The distilled water is heated to 70°C. The hydroxyethylcellulose, benzoic acid and tartaric acid are dissolved therein with stirring. The mixture is cooled to ambient temperature and the glycerol and sorbitol solution are added with stirring. At ambient temperature the active substance is added and stirred until completely dissolved. The syrup is then evacuated of any air with stirring.

CLAIMS

1. A compound of formula I



(I)

(wherein
A represents a $-CH_2-CH_2-$, -CH=CH-, $-\overset{*}{C}H_2-CO-$ or $-\overset{*}{N}H-CO-$ group, and

B represents a methylene, carbonyl or thiocarbonyl group, or

A represents a $-CO-CO-$ or $-\overset{OH}{\overset{|}{\overset{*}{C}}}H-CO-$ group and B represents a methylene group, the mark * signifying that the carbon or nitrogen atom so marked is bonded to the phenyl ring;

E represents a straight-chained alkylene group with 1 to 3 carbon atoms optionally substituted by an alkyl group with 1 to 3 carbon atoms;

G represents a group G_1G_2 optionally substituted by an alkyl group with 1 to 3 carbon atoms and wherein G_1 represents a straight-chained alkylene group with 1 to 5 carbon atoms and G_2, which is adjacent to the phenyl ring, represents a bond linking G_1 to the phenyl ring or, where G_1 represents a straight-claimed alkylene group with 2 to 4 carbon atoms, an oxygen or sulphur atom or an imino, methylimino, sulphinyl or sulphonyl group;

R_1 represents a hydrogen or halogen atom or, a trifluoromethyl, nitro, amino, alkylamino, dialkylamino, alkyl, hydroxy, alkoxy or phenylalkoxy group, wherein any alkyl moiety in R_1 contains from 1 to 3 carbon atoms, and

R_2 represents a hydrogen or halogen atom, or a hydroxy, alkoxy, phenylalkoxy or alkyl group, wherein any alkyl moiety in R_2 contains from 1 to 3 carbon atoms, or

R_1 and R_2 together represent an alkylenedioxy group with 1 or 2 carbon atoms;

R_3 represents a hydrogen or halogen atom, or an alkyl group with 1 to 3 carbon atoms, or an alkoxy group with 1 to 3 carbon atoms, or a hydroxy, nitro, cyano or trifluoromethyl group, and

R_4 represents a hydrogen atom, or an amino group, or an alkoxy, alkanesulphonyloxy, alkylamino or dialkylamino group with 1 to 3 carbon atoms in the or each alkyl moiety or an alkanoylamino group with 2 or 3 carbon atoms in the alkanoyl moiety; or

R_3 and R_4 together represent an alkylenedioxy group with 1 or 2 carbon atoms;

R_5 represents a hydrogen or halogen atom, or a hydroxy group, or an alkyl or alkoxy group with 1 to 3 carbon atoms in the alkyl moiety;

m represents the number 1, 2, 3, 4 or 5, and

n represents the number 0, 1 or 2, with the proviso that the sum of n and m is 3, 4 or 5);

the enantiomers, diastereomers and acid addition salts thereof.

2. A compound formula as claimed in claim 1, wherein

A, B, m and n are as defined in claim 1;

E represents a methylene or ethylene group;

G represents a group G_1G_2 wherein G_2 represents a bond and G_1 represents an n-alkylene group with 1 to 4 carbon atoms, or wherein G_1 represents an ethylene or n-propylene group and G_2 represents an oxygen or sulphur atom or an imino, methylimino, sulphinyl or sulphonyl group;

R_1 represents a hydrogen, fluorine, chlorine or bromine atom, or a hydroxy, methoxy, trifluoromethyl, methylamino or dimethylamino group, and

R_2 represents a hydrogen, chlorine or bromine atom or a methoxy group, or

R_1 and R_2 together represent a methylenedioxy group;

R_3 represents a hydrogen, fluorine, chlorine or bromine atom or a methyl, hydroxy, methoxy or nitro group, and

R_4 represents a hydrogen atom or a methoxy, methanesulphonyloxy, amino or acetylamino group, or

R_3 and R_4 together represent a methylenedioxy group; and

R_5 represents a hydrogen, chlorine or bromine atom

or a methoxy group;

and the enantiomers, diastereomers and acid addition salts thereof.

3. A compound of formula I as claimed in claim 1, wherein

m and n are as defined in claim 1;

A represents a $-CH_2CH_2-$ or -CH=CH- group and B represents a methylene or carbonyl group, or

A represents a -CO-CO- group and B represents a methylene group;

E represents a methylene or ethylene group;

G represents an n-alkylene group with 2 to 4 carbon atoms, or an ethyleneoxy or n-propyleneoxy group;

R_1 represents a hydrogen atom or a methoxy group, and

R_2 represents a hydrogen atom or a methoxy group , or

R_1 and R_2 together represent a methylenedioxy group;

R_3 represents a hydrogen atom or a methyl, hydroxy or methoxy group, and

R_4 represents a hydrogen atom or a methoxy group, or

R_3 and R_4 together represent a methylenedioxy group; and

R_5 represents a hydrogen atom;

and the enantiomers, diastereomers and acid addition salts thereof.

4. The compound 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-3-yl)-methyl]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one or an enantiomer or acid addition salt thereof.

5. The compound 3-[(N-(2-(3,4-dimethoxy-phenyl)-ethyl)-piperidin-2-yl)-ethyl-2]-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3 benzazepin-2-one or an enantiomer or acid addition salt thereof.

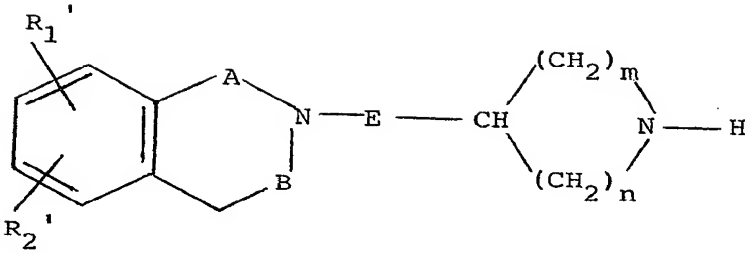
6. A compound as claimed in any one of claims 1 to 5 being a physiologically acceptable acid addition salt of a compound of formula I.

7. A pharmaceutical composition comprising a compound of formula I as claimed in any one of claims 1 to 5 or a physiologically acceptable acid addition salt thereof together with at least one pharmaceutical carrier or excipient.

8. A process for preparing a compound of formula I as claimed in claim 1, which comprises at least one of the following steps:

a) reacting a compound of formula II

B



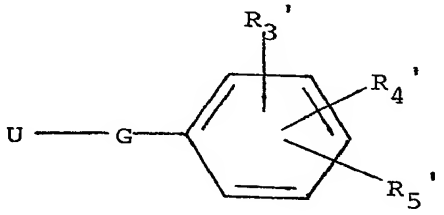
(II)

(wherein

A, B, E, m and n are as defined in claim 1,

R_1' represents a hydroxy, amino or C_{1-3} alkylamino group protected by a protecting group or has the meanings given for R_1 in claim 1, and

R_2' represents a hydroxy group protected by a protecting group or has the meanings given for R_2 in claim 1) with a compound of formula III



(III)

(wherein

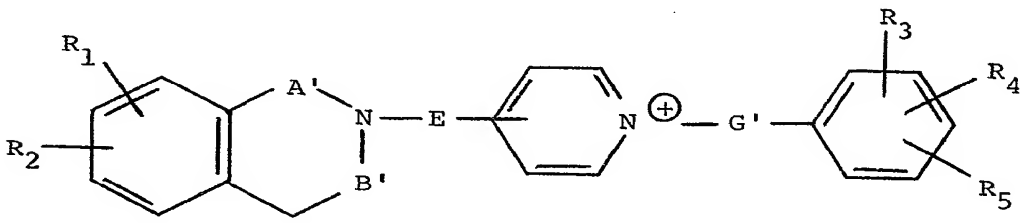
R_3' represents a hydroxy group protected by a protecting group or has the meanings given for R_3 in claim 1,

R_4' represents an amino or C_{1-3} alkylamino group protected by a protecting group or has the meanings given for R_4 in claim 1,

R_5' represents a hydroxy group protected by a protecting group or has the meanings given for R_5 in claim 1, and

U represents a nucleophilic leaving group) and subsequently, if required, splitting off any protecting group used;

b) (to prepare a compound of formula I wherein G has the meanings given for G in claim 1,(with the exception of the groups containing a sulphenyl, sulphinyl or sulphonyl group), A represents a $-CH_2-CH_2-$ group, B represents a methylene or carbonyl group and the sum of m and n is 4) hydrogenating a compound of formula IV



(IV)

(wherein

R_1 to R_5 and E are as defined in claim 1,

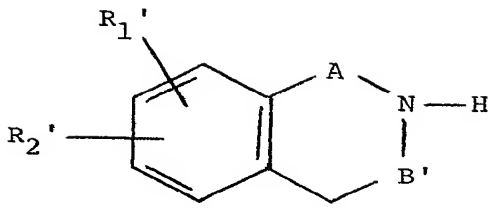
G' has the meanings given for G in claim 1 with the exception of the groups containing a sulphur atom or a sulphinyl or sulphonyl group,

A' represents a -CH=CH- or $-CH_2CH_2-$ group, and

B' represents a methylene or carbonyl group);

c) (to prepare a compound of formula I wherein B represents a carbonyl or methylene group) reacting a compound of formula V

B'



(V)

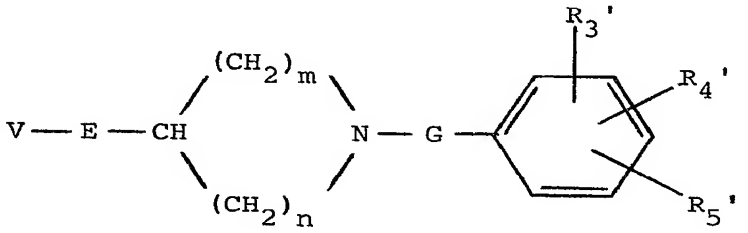
(wherein

A is as defined in claim 1,

R_1' represents a hydroxy, amino or C_{1-3} alkylamino group protected by a protecting group or has the meanings given for R_1 in claim 1,

R_2' represents a hydroxy group protected by a protecting group or has the meanings given for R_2 in claim 1, and

B' represents a carbonyl or methylene group) with a compound of formula VI



(VI)

(wherein

E, G, m and n are as defined in claim 1,

R_3' represents a hydroxy group protected by a protecting group or has the meanings given for R_3 in claim 1,

R_4' represents an amino or C_{1-3} alkylamino group protected by a protecting group or has the meaning given for R_4

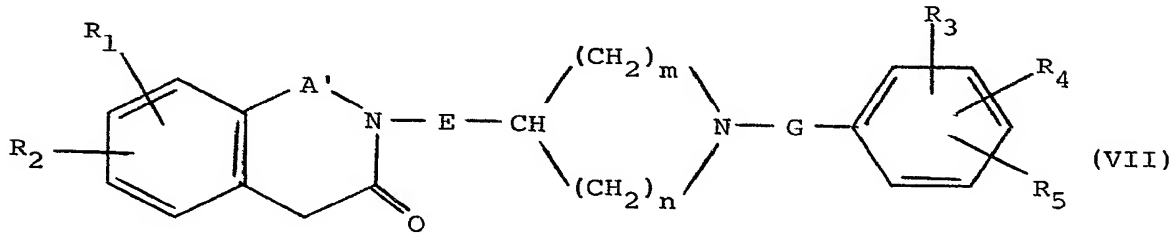
B

in claim 1,

R_5' represents a hydroxy group protected by a protecting group or has the meanings given for R_5 in claim 1, and

V represents a nucleophilically exchangeable group) and subsequently, if required, splitting off any protecting group used;

d) (to prepare a compound of formula I wherein A represents a $-CH_2-CH_2-$ or -CH=CH- group and B represents a thiocarbonyl group) reacting a compound of formula VII



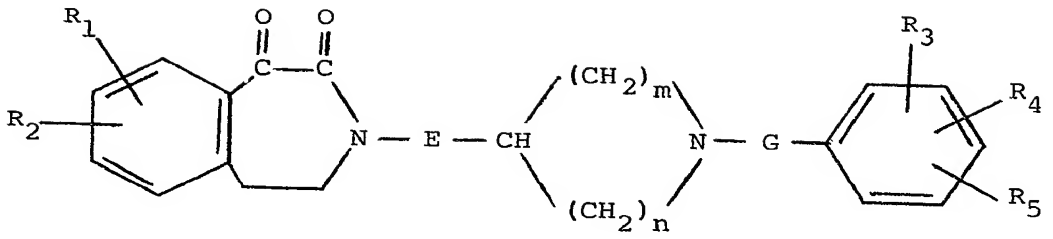
(VII)

(wherein

R_1 to R_5, E, G, m and n are as defined in claim 1 and A' represents a $-CH_2-CH_2-$ or -CH=CH- group) with a sulphurising agent;

e) (to prepare a compound of formula I wherein A represents a $-\underset{OH}{CH}-CO-$ group and B represents a methylene group) reducing a compound of general formula VIII

B

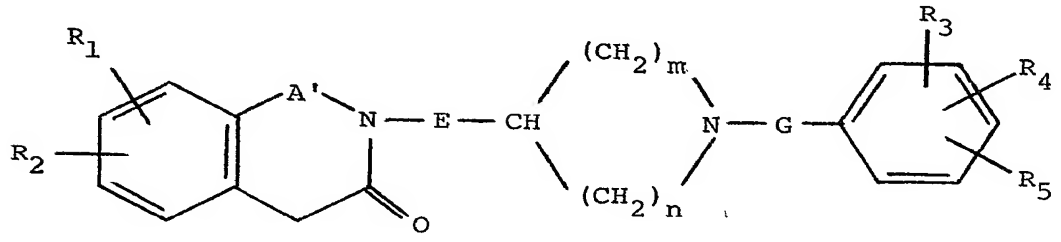


(VIII)

(wherein

R_1 to R_5, E, G, m and n are as defined in claim 1);

f) (to prepare a compound of formula I wherein A represents a $-CH_2-CH_2-$ or -CH=CH- group and B represents a methylene group) reducing a compound of formula IX



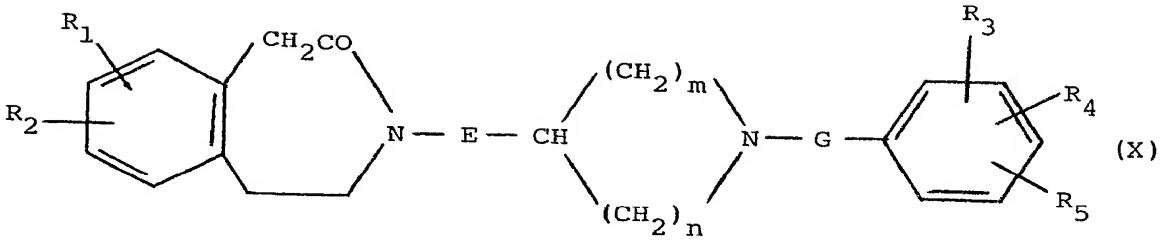
(IX)

(wherein

R_1 to R_5, E, G, m and n are as defined in claim 1 and A' represents a $-CH_2-CH_2-$ or -CH=CH- group);

g) (to prepare a compound of formula I wherein A represents a -COCO- group) oxidizing a compound of formula X

B

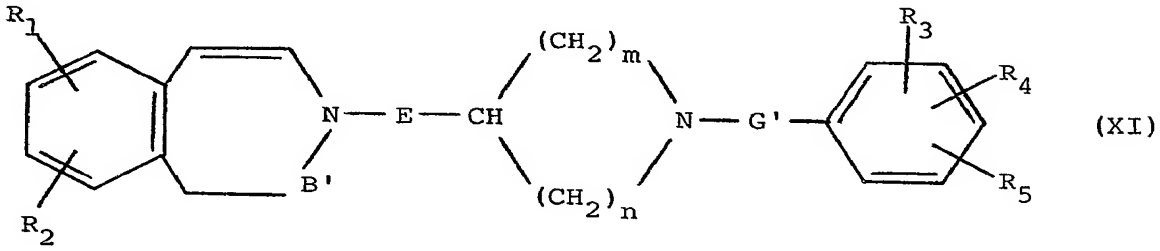


(X)

(wherein

R_1 to R_5, E, G, m and n are as defined in claim 1);

h) (to prepare a compound of formula I wherein G has the meaning given for G in claim 1 (with the exception of the groups containing a sulphur atom or a sulphinyl or sulphonyl group), A represents a $-CH_2-CH_2-$ group and B represents a methylene or carbonyl group) hydrogenating a compound of formula XI



(XI)

(wherein

R_1 to R_5, E, m and n are as defined in claim 1,

G' has the meaning given for G in claim 1, with the exception of the groups containing a sulphur atom or a sulphinyl or sulphonyl group, and

B' represents a methylene or carbonyl group);

i) reducing a compound of formula I wherein R_1 and/or R_3 represents a nitro group to a corresponding amino compound of

B1

formula I;

j) acylating a compound of formula I wherein R_4 represents a hydroxy or amino group to a corresponding alkane-sulphonyloxy or alkanoylamino compound of formula I;

k) resolving a compound of formula I which contains at least one chiral centre into its diastereomers or into its enantiomers; and

l) converting a compound of formula I into an acid addition salt thereof.

9. A process as claimed in claim 8 wherein A, B, m and n, are as defined in claim 8,

E represents a methylene or ethylene group;

G represents a group G_1G_2 wherein G_2 represents a bond G_1 represents an n-alkylene group with 1 to 4 carbon atoms, or wherein G_1 represents an ethylene or n-propylene group and G_2 represents an oxygen or sulphur atom or an imino, methylimino, sulphinyl or sulphonyl group;

R_1 represents a hydrogen, fluorine, chlorine or bromine atom, or a hydroxy, methoxy, trifluoromethyl, methylamino or dimethylamino group, and

R_2 represents a hydrogen, chlorine or bromine atom or a methoxy group, or

R_3 represents a hydrogen, fluorine, chlorine or bromine atom or a methyl, hydroxy, methoxy or nitro group, and

R_4 represents a hydrogen atom or a methoxy, methane-sulphonyloxy, amino or acetylamino group, or

R_5 represents a hydrogen, chlorine or bromine atom or a

methoxy group.

10. A process as claimed in claim 8 wherein m and n are as defined in claim 8

A represents a $-CH_2CH_2$ or -CH=CH- group and B represents a methylene or carbonyl group, or

A represents a -CO-CO- group and B represents a methylene group;

E represents a methylene or ethylene group;

G represents an n-alkylene group with 2 to 4 carbon atoms, or an ethyleneoxy or n-propyleneoxy group;

R_1 represents a hydrogen atom or a methoxy group, and

R_2 represents a hydrogen atom or a methoxy group, or

R_3 represents a hydrogen atom or a methyl, hydroxy or methoxy group, and

R_4 represents a hydrogen atom or a methoxy group, or

R_5 represents a hydrogen atom.

11. A process as claimed in claim 8 wherein A represents $-CH_2-CO-$, B represents methylene, one of m and n is 1 and the other is 3, E represents methylene, G represents ethylene, R_1 represents 7-methoxy, R_2 represents 8-methoxy, R_3 represents 3-methoxy, R_4 represents 4-methoxy and R_5 represents hydrogen.

12. A process as claimed in claim 8 wherein A represents $-CH_2-CO-$, B represents methylene, m is 3, n is 0, E represents ethylene, G represents ethylene, R_1 represents 7-methoxy, R_2 represents 8-methoxy, R_3 represents 3-methoxy, R_4 represents 4-

methoxy and R_5 represents hydrogen.

13. A process as claimed in claim 8 wherein the reaction is carried out in a solvent.

14. A process as claimed in claim 8 or 13 wherein the reaction of either of steps (a) and (c) is carried out in the presence of an acid-binding agent.

15. A process as claimed in claim 8 or 13 wherein in reaction step (a) or (c) protecting groups are split off by hydrolysis or hydrogenolysis.

16. A process as claimed in claim 8 or 13 wherein the reaction of step (a) or (c) is carried out at temperatures of between 0 to 150°C.

17. A process as claimed in claim 8 or 13 wherein the catalytic hydrogenation of step (b) or (h) is carried out under a hydrogen pressure of from 1 to 7 bar, and at a temperatures of between 0 and 75°C.

18. A process as claimed in claim 8 or 13 wherein the reaction of step (d) is carried out using a sulfurizing agent selected from phosphous pentasulphide and 2,4-bis(4-methoxy-phenyl)-1,3-dithia-2,4-diphosphentan-2,4-disulphide.

19. A process as claimed in claim 8 or 13 wherein the

C

reaction of step (d) is carried out at temperatures of between 50 and 150°C.

20. A process as claimed in claim 18 wherein the reaction of step (d) is carried out at temperatures of between 50 and 150°C.

21. A process as claimed in claim 8 or 13 wherein the reaction of step (e) is carried out with a metal hydride.

22. A process as claimed in claim 8 or 13 wherein the reaction of step (e) is carried out at temperatures of between 0 and 80°C.

23. A process as claimed in claim 21 wherein the reaction of step (e) is carried out at temperatures of between 0 and 80°C.

24. A process as claimed in claim 8 wherein the reaction of step (f) is carried out with a metal hydride or with a complex of diborane and a thioether.

25. A process as claimed in claim 8 or 13 wherein the reaction of step (f) is carried out at temperatures of between 0 and 25°C.

26. A process as claimed in claim 24 wherein the reaction of step (f) is carried out at temperatures of between 0 and 25°C.

27. A process as claimed in claim 8 or 13 wherein the

oxidation of step (g) is carried out with potassium permanganate, selenium dioxide or sodium dichromate.

28. A process as claimed in claim 8 or 13 wherein the oxidation of step (g) is carried out at temperatures of between 0 and 100°C.

29. A process as claimed in claim 27 wherein the oxidation of step (g) is carried out at temperatures of between 0 and 100°C.

30. The use of a compound of formula I, as defined in any one of claims 1 to 5, or a physiologically acceptable acid addition salt thereof for the treatment of the human or non-human animal body to combat sinus tachycardia or ischaemic heart disease.

31. A process for preparing a pharmaceutical composition which comprises admixing a compound of formula I, as defined in any one of claims 1 to 5 or a physiologically acceptable acid addition salt thereof, with a pharmaceutically acceptable carrier or excipient.

32. A commercial package containing, as active pharmaceutical ingredient, a compound as claimed in any one of claims 1 to 5 or a physiologically acceptable acid addition salt

thereof, together with instructions for use in treatment of the human or non-human animal body to combat sinus tachycardia or ischaemic heart disease.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente